REMARKS

The Office Action dated August 1, 2006 has been reviewed carefully and all of the claims have been amended directly or indirectly in a sincere effort to place the application in condition for allowance. New Claims 55 through 118 has been added. In addition, certain clarifying amendments had been re-entered (copied and pasted to the specification) from material contained in the related Provisional Application Serial No. 60/319,436. Reconsideration of the prior rejection and allowance of the amended claims are respectfully requested.

THE INVENTION

The present invention has solved a long standing and previously unsolved problem which is of great importance to the mental health and survival of patients.

The methods of the present invention provide prompt, initial, effective treatment of, in one embodiment, patients suffering major depressive disorders, as that term is defined in the specification at page 11, lines 4 to 18, with a particular emphasis on initial treatment of the patient by administering an antidepressant drug in combination with an antipsychotic drug, wherein the major depressive disorder is categorized as non-treatment resistant and non-psychotic. This embodiment is expressed in independent method Claim 1 and the claims which depend directly or indirectly therefrom. Patients of particular interest are persons having depression who are at high risk of suicide. However, all depressed patients are at risk of suicide.

In another embodiment, as recited in independent method Claim 2 and the claims which depend therefrom, the patient suffering from unipolar depression which is categorized as non-treatment resistant and non-psychotic, is subjected to initial treatment by combination of an effective amount of antidepressant in combination with an antipsychotic drug.

In a further embodiment of the invention, as set forth in independent Claim 3, a nonpsychotic patient having cognitive distortions with functional impairment or health hazards or a patient undergoing smoking cessation or nicotine withdrawal is

administered an effective amount of an antidepressant in combination with an antipsychotic drug.

Among the benefits provided by Applicant's invention are the prevention of disease progression, modification of the course of depression, delaying or preventing relapse or recurrence of depression, resisting the development of delusional/psychotic depression, remedying the development of tolerance toward the antidepressant and resisting the antidepressant's paradoxial effect of sensitizing patients to depression and relapse, as well a resisting the worsening of depressions caused by antidepressants.

Claim 6 - Section 112

In response to the rejection of Claim 6 based upon the inclusion in the list of antipsychotic drugs of "ORG 5222" "SM 9018", and "JL-13" Applicant has amended Claim 6 to delete these three recitals.

Claims 1-3, 7, 8, 11-12, 19, 23, 27 and 31 – Section 112

These claims have been rejected under the first paragraph of Section 112. The Examiner in this context states that the claims are enabling for method of treating depression, cognitive distortions, smoking cessation or nicotine withdrawal, by administering certain antidepressants as defined in the specification and in prior art in combination with certain atypical antipsychotic drugs known to be useful for improving therapeutic outcomes in depression. The Examiner, however, has stated that the specification does not reasonably provide for such a method for any antidepressant and any antipsychotic in accordance with the eight factor test of *In re Wands*.

(We have further addressed this in the line by line reply)

Of primary importance in this context is the fact that one skilled in the art of the present invention is not nearly a handyman garage tinkerer, but rather is a highly educated individual who has performed well enough in undergraduate education to be accepted into medical school, has performed well enough in medical school to graduate and to be accepted into the appropriate internship and residency program, and has become board certified in the specialty of psychiatry. In addition, one skilled in the art would have experience in the field treating various types of patients with use of appropriate drugs being the appropriate conditions. In the present case, with the treatment of the above described conditions as are enabled and the identification of the generic categories of goods, coupled with the extensive listing of specific drugs which are preferred, the extensive examples provided, and other guidance in the text, it is respectfully submitted that one skilled in the art would clearly have no need to engage in undue experimentation in order to select drugs from each category for the initial treatment of the non-psychotic and in some instances, non-treatment resistant patients for the recited methods of independent Claims 1 through 3. Further, Applicant has stated in detail the preference for low dosage and as defined "effective amount" on lines 1-18 of page 9 of the specification.

Further, as the Examiner has acknowledged the prior art has recognized the utility of atypical antipsychotic drugs for their previous uses in treating depression (e.g. psychotic depression, TRD), one skilled in the art would have this information. This is of importance in the enablement context.

Applicant respectfully disagrees with respect to the Examiner's statement on page 5 that the state of the art is unpredictable. The use of antidepressant and antipsychotic

drugs for other indications has been known for a long time, such as for psychotic depression, for example. There are numerous antidepressants on the market which are well known and used in treating psychotic patients for depression.

It is also well known to those skilled in the art that once medication has been approved by the United States FDA for any reason or indications, licensed physicians can use that medication "off label" without requiring the sort of experimentation, toxicology, animal studies and clinical studies required for the initial approval of the drug for a particular purpose. To employ such a medication off label in a non-FDA approved dose or indication, the clinicians rely on their skill, experience and where appropriate, guidance obtained from others. This common off label use does not require undue experimentation, but rather a matter of professional judgment on the part of the physician (based on the currently available information) and the evaluation or risk versus benefit and alternatives analysis. In the present case, as the drugs are known and approved (or as they are becoming approved) for use, for example, in treating psychotic depression, they are known and used by those skilled in the art to treat such patients, but have not been known to be employed in the combination and for the specific refined purpose as set forth in Applicant's Claims 1 through 3.

With respect to Claims 7, 8, 11-12, 19, 23, 27 and 31, as these clearly recite certain preferred drugs and combinations thereof for use in the process, it is respectfully submitted that these claims are congruent with the specification and do not fall into the objected to category of "involving any antidepressant and any antipsychotic" and, therefore, are not subject to an objection based upon a lack of enablement. One skilled in

the art would clearly know from the specification and claims the identity of the drug, the preferred dosage and the use of initial treatment.

(We have further addressed this concern in the line by line reply).

It is important to bear in mid this context that a clinician may have questions regarding the practice of the invention, the answers to which (with the specifications) are well within the skills of one of ordinary skill in the art. Such questions, particularly when combined with what is known in the art, do not necessarily rise to the level of requiring undue experimentation. It is respectfully submitted that the present disclosure when compared with the amended prior claims and the newly introduced claims satisfies the enablement standard.

It is also important to bear in mind that when dealing with known pharmaceuticals which have received United States FDA approval, the required testing to obtain such approval has been achieved. This is not, therefore, a situation wherein newly created pharmaceutical compounds without an adequate understanding of the safety efficacy of the same are involved, but rather known compounds which through FDA approval contribute meaningfully to the knowledge of the clinician regarding the compounds. In the more specific dependent claims, the individual compounds and combinations thereof in each category are specifically recited thereby clearly satisfying the enablement requirement.

It is also important to bear in mind that the focal point of the present claims is treatment of patients at any stage and not prophylactic preventive action on people who never ever had depression.

It is respectfully submitted, therefore, that with Applicant's extensive disclosure combined with what one in the art would know, undue experimentation would not be required to practice Applicant's invention as set forth in Claims 1 through 3 and that no experimentation of any consequence would be required in the connection with the specific recitals of the other claims in this grouping (Claims 7, 8, 11, 12, 14, 23, 27 and 31). Withdrawal of the enablement objection to the claims in this group is respectfully requested.

Claims 42, 48, 53 and 54 – Section 112

These claims were stated by the Examiner to be enabling for the method of treating depression and associated conditions, but not enabling for preventing depression or the progression or relapse thereof.

(We have further addressed this concern in the line by line reply, and Appendix B of our reply).

It is respectfully submitted that withdrawal of the prevention aspect from these claims obviates the enablement rejection and that the claims therefore are allowable. The comments made hereinbefore in respect of enablement in general are equally applicable at this juncture.

Claims 1-2, 4-6, 9, 11, 13, 14, 16, 18, 20-22, 24-26, 28-30, 32-35, 37-38, 42, 48, 49, 51, 53 and 54 – Section 102(b)

These claims were rejected as allegedly being anticipated by Tollefson (WO 99/61027) on the basis of Tollefson disclosing a method of treating depression by administering both a serotonin reuptake inhibitor and an atypical antipsychotic. *(We have further addressed this concern in the line by line reply).*

Tollefson discloses the use of a combination of drugs, such as an atypical antipsychotic drug and a serotonin reuptake inhibitor in treatment resistant depression. There is no disclosure of patients who have not had Treatment Resistant Depression (TRD). This is to be contrasted with Applicant's amended independent Claim 1, which is a method of treating a patient suffering from major depressive disorder by administering a treatment as an initial treatment, as soon as possible, upon presentation of the patient to a physician or health care provider. The treatment involves administration of an antidepressant in combination with an antipsychotic drug, wherein the major depressive is categorized as "non-treatment resistant (see page 3, lines 25-28 of the specification) and non-psychotic". This clearly is distinguishable from the teaching of Tollefson.

Similarly, Claim 2 recites an initial treatment of a patient suffering from unipolar depression by administering an effective amount of an antidepressant in combination with an antipsychotic drug with the unipolar depression being characterized as "non-treatment resistant and non-psychotic". The treatment is provided as an initial treatment, as soon as possible, upon presentation of the patient to a physician or health care provider. This is clearly distinguishable from Tollefson, which cannot be said to anticipate Claims 1 and 2.

While Claim 3 has not been directly rejected, in this series claims which due to multiple dependency, depend directly or indirectly from Claim 3 are in the group

rejected. Claim 3 does not recite depression, but rather is directed for a non-psychotic patient being treated for cognitive disorders with functional impairment or health hazards as an initial treatment, or is directed for a non-psychotic patient undergoing smoking cessation or nicotine withdrawal. In the treatment an effective amount of antidepressant in combination with antipsychotic drug is being provided. Cognitive distortion cannot be equated with depression.

In view of the foregoing, it is respectfully submitted that none of the claims in this grouping, all of which depend directly or indirectly from Claims 1, 2 or 3 are anticipated by Tollefson.

Dependent Claims within this grouping

A number of the dependent claims are not asserted as independently contributing to patentability apart from their direct or indirect dependency from Claims 1, 2 or 3, or in some instances other claims. Several dependent claims in this grouping do add unique features.

Claim 7 recites the antipsychotic drug being a dopamine system stabilizer. Claim 8 recites aripriprazole as a specie thereof.

Claim 9 recites an antipsychotic drug administered in a low dose, which is expanded upon in the definition of "effective amount" as set forth on Page 9, Lines 1-18. This claimed, preferred dose is not taught or suggested by Tollefson.

Claim 9 recites an antipsychotic drug administered in a low dose, which is expanded upon in the definition of "effective amount" as set forth on page 9, lines 1-18. This is not taught or suggested by Tollefson.

Claim 11 recites a Markush grouping of preferred serotonin reuptake inhibitors.

Claims 16-18 recite specific combinations of antidepressant and antipsychotic drugs which, even if listed individually in a "laundry list" of possibilities in Tollefson, is not taught by Tollefson, and, therefore, is not anticipated by Tollefson. The same is true with respect to the antidepressant combinations recited in dependent Claims 20 through 22, as well as the antidepressant and antipsychotic combinations recited in Claims 24 through 26 and 28 through 30. The antidepressant combinations recited in Claims 32 through 35 are also not specifically taught in Tollefson.

The dependent claims which have not been expressly discussed herein are asserted as being patentable based upon dependency from allowable claims.

It is respectfully submitted that Tollefson does not render this group of claims unpatentable under Section 102(b) for reasons which have been stated hereinbefore.

Claims 1-2, 4-6, 9-11, 13-14, 37-38, 42, 48, 51, 53 and 54 – Section 102(e)

These claims were rejected as allegedly being anticipated by Faour, U.S. Publication 2001/0048943 for disclosing a method of treating depression, anxiety and/or psychosis in a mammal.

The Faour reference discloses a delivery device which is said to be useful in treating depression, anxiety or psychosis related disorders. It is respectfully submitted that one skilled in the art would not in any manner find any teaching or suggestion which renders Applicant's methods of independent Claims 1, 2 and 3 as hereinbefore discussed, wherein the disorder is recited as being non-psychotic. Further the major depressive disorder of Claim 1 is characterized as being an initial treatment for the depressive disorder which is non-treatment resistant as is the unipolar depression of Claim 2. There

is no teaching or suggestion whatsoever in Faour of any such method as contrasted with his specific teaching of a delivery device with broad general terms as to the mode of employment.

Further, there is no disclosure in Faour of Applicant's initial treatment, as soon as possible, upon presentation to a physician or other health care provider.

Dependent Claims

The comments made hereinbefore in respect of dependent Claims 4-6, 9, 11, 13, 14, 37, 38, 42, 48, 51, 54 are equally applicable at this juncture. The claim in the present grouping not present in the prior grouping is Claim 10. Claim 10 recites certain specifically preferred antipsychotic drugs for use in Applicant's combination and is not asserted as being independently contributing to patentability apart from its dependency of on Claim 9 with its recital of low dose as defined in the specification, which depends alternatively from Claims 1, 2 and 3.

It is respectfully submitted that this group of claims is not anticipated by the Faour disclosure.

Claims 3-6, 9, 49, 50 and 51 – Section 102(a)

These claims were rejected as allegedly being anticipated by George et al. publication George discloses the use of Bupropion in a test for smoking cessation in patients with schizophrenic disorders.

It is noted that the George article bears a copyright notice with the year date "2002". Applicant's undersigned attorney cannot find in the document an indication

of the precise date when it was published. On page 60, there is reference to the material having been "presented in part at 7th Annual Meeting of the Society for Research on Nicotine and Tobacco, Seattle Washington, March 23-25, 2001 and the 40th Annual Meeting of the American College of Neuropsychopharmacology, Waikoloa, Hawaii, December 9-13, 2001". As there is no delineation as to what was and what was not published, as to what portion of the publication was presented at each meeting, and the actual publication appears to be in 2002, it is respectfully submitted that it is not clear that this is prior art against Applicant's application, which claims priority from Provisional Application Serial No. 60/319,436, filed July 30, 2002. The reference does not contain information which otherwise would establish the publication date. On this basis, it is respectfully requested that this publication be removed as prior art until such time as it can be confirmed that the publication date antedates Applicant's Provisional Application filing date. At the bottom of column 1 on the first page there is an indication as to the publication having been accepted on January 2, 2002, but no indication regarding the date of publication.

In the interest of providing a complete response without admitting that the George publication is prior art, Applicant offers the following comments. The comments made hereinbefore with respect to Claim 3 through 6, as well as the low dose recital of Claim 9 and the comments regarding Claims 49 and 52 are equally applicable at this juncture. With regard to Claim 50, this focuses on the smoking cessation or nicotine withdrawal portion of independent Claim 3.

George's sole objective is to determine the impact of bupropion on schizophrenic patients in respect of smoking cessation. Applicant's independent Claim 3

is directed toward non-psychotic patients as called for in of Claim 3. We had more specifics in the line by line reply for Claim 3 as amended.

Claims 1-2, 4, 7, 9, 11-15, 37, 38, 42, 48 and 51-54 – Section 102(e)

These claims were rejected on the basis of Chappell, U.S. Publication 2002/0094986 under Section 102(e).

Before turning to the substance of this portion of the Office Action, it is noted that on line 1 of the second paragraph on page 14, Claim 3 is not listed, but is contained within the listing on line 6. Also, Claim 49 is not listed on line 1, but is identified on line 7. Finally, Claims 51-54 are listed on line 1, but are not identified in the remainder of the paragraph.

Chappell discloses a method for treating depression, anxiety or psychosis in a mammal by administering an antidepressant and a D4 receptor antagonist and a pharmaceutically acceptable carrier.

It is noted first of all that unlike Applicant's independent Claims 1 and 2, Chappell does not treat patients suffering from major depressive disorders (Claim 1) or unipolar depression (Claim 2) with the depressive disorder or depression being characterized as non-treatment resistant and non-psychotic and further does not emphasize initial treatment which is an important contribution as recited in these two claims. Further, Claim 3 also deals with treating a non-psychotic patient with an initial treatment for the purposes set forth in Claim 3, i.e., cognitive distortions with functional impairment or health hazard or non-psychotic patient for smoking cessation or nicotine

withdrawal. The comments made hereinbefore in respect of Claims 4, 9, 11, 13, 14, 37, 38, 42, 48, 51, 53 and 54 are equally applicable at this juncture.

With respect to the claims in this grouping not discussed hereinbefore and subject to the analysis of this paragraph in respect of claim numbers set forth herein, Claim 8, 12, 15 and 52 will be considered. Claim 8 depends from Claim 7 and recites the dopamine system stabilizer being Aripiprazole or pharmaceutically acceptable salts thereof. With respect to Claim 9, there is no focus on low dose in Chappell as described in the effective amounts definition on page 9, lines 1 through 18, of Applicant's specification. Claim 12 recites a Markush grouping of preferred antidepressants. Dependent Claim 15 recites the antidepressant being Clomipramine and Claim 52, which depends from 13, also recites this compound.

In summary, it is respectfully submitted that independent Claims 1, 2 and 3 possess novelty over Chappell and that certain dependent claims enhance patentability to the recitals thereof. It is respectfully requested the Section 102(e) rejection of this group of claims be withdrawn.

Claims 3, 36, 39, 41, 43 and 49 - Section 103(a)

These claims were rejected as allegedly unpatentable over Tollefson (WO 99/61027). The Examiner has stated that Tollefson (a) does not disclose a method in which the antipsychotic is administered according to the dosage levels disclosed in Claim 36 and (b) does not disclose a method of administering treatments as soon as possible, or (c) a method wherein treatment is given for preventing suicide. The Examiner further states that Tollefson does not explicitly disclose the method of treating cognitive

distortions as defined in Applicant's specification. The Examiner then goes on to provide an analysis which leads to his conclusion that the features in this group of claims would have been obvious over Tollefson. Applicant respectfully traverses this conclusion.

First of all, Claim 3 as amended makes reference to the method being applied to non-psychotic patients and as regards to cognitive distortion as an initial treatment. The combination of antidepressant and an antipsychotic drug under these conditions is not suggested by Tollefson in respect of the recited objectives of Claim 3, cognitive distortions with functional impairment or health hazards or a patient undergoing smoking cessation or nicotine withdrawal. It is respectfully submitted that in view of the great medical importance of the problem solved by Applicant as set forth in Claim 3, were there an obvious solution rather than allowing these potentially serious ongoing problems to exist in a patient, the obvious solution would have been adopted. Combined with absence of such a solution in the cited art, it would appear that no such solution has been forth coming prior to Applicant's invention. It is respectfully submitted therefore that Claim 3 is allowable over Tollefson.

With respect to Claim 36, the specific ranges of dosage claimed by Applicant are not taught or suggested by Tollefson.

The initial treatment or as soon as possible upon presentation is also not taught or suggested by Tollefson, despite the importance of such treatment. Claim 39 is dependent from Claim 1 or 2 and the comments made hereinbefore with respect to those claims are equally applicable at this juncture. It is respectfully submitted that Claim 39 is not obvious over Tollefson.

Claim 41 is dependent from Claim 1 or 2 with the focus on the prevention of suicide, thereby enhancing the criticality of the recitals of those claims in respect of non-treatment resistant, non-psychotic initial treatment is of great importance.

The same is true with respect to Claim 43, which has been amended to depend from Claim 3.

Claim 49 is directed toward cognitive distortions leading to functional impairment or serious health hazard. This, too, would have surfaced long ago had Tollefson rendered such an approach obvious. It is respectfully submitted that claims 3, 36, 39, 41, 43 and 49 are allowable under Section 103(a).

New Claims 55 through 118, in general, refine the recitals of prior claims either through dependency or parallel recitals. Please note that as regards to claims 59, 60 and 62 the definition of for the "benefit of the group" had been defined in the Amendments to the specification of the utility -Guidance 2a) that had been pasted from the provisional application.

SUMMARY AND CONCLUSIONS follows on page 101.

"The line by line reply" to the 1st office action

In this **line by line** reply to the 1st office action, for better organization, we put our brief reply in a tables Indented to the left or left column is the copy of the 1st office action's pertinent part, indented to right or right column is reference or our brief reply.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites a list of antipsychotic drugs, including, ORG 5222 and SM-9018. These names do not clearly and distinctly indicate a particular chemical compound, thus rendering the listing of drugs indefinite.

Reply-1: The examiner starts with the rejection of claim 6 being indefinite.

We will amend claim 6 by deleting **ORG 5222** and **SM-9018**, and with the same logic **delete JL-13**.

However, professional publications were referring to ORG 5222, SM-9018, and JL-13 compounds as such. Since these were published for the professional audience, those skilled in the field of drug or medication development should have been able to identify these compounds by these names. If for trade secret or other reasons they did not yet made the compound structure public, when they would make it public in the future (and would need to file necessary papers about prior experiments to FDA) the above names would identify these compounds at that time. Never the less we complied with the examiner's request by amending claim 6.

Claims 1-3, 7, 8, 11-12, 19, 23, 27, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art in combination with certain specific atypical antipsychotic drugs known to be useful for improving therapeutic outcomes in depression, **does not reasonably provide enablement** for such a method involving **any antidepressant and any antipsychotic.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Reply-2: If the examiner have referenced the "drugs known to be useful" to give us credit for the fact that we did not invent the compounds, but that they are known and that their utility is known, than this paragraph with the following eight sentences can be disregarded in this box (ending with the reference to "Reply-14). Otherwise, we would like to start with that the examiner's underlined comment that "prior art in combination with certain specific atypical antipsychotic drugs known to be useful for improving therapeutic outcomes in depression", is potential for misunderstanding. We have described in our utility in great details of what types of depression the combination therapy had been useful, and also that why the use of antipsychotics in these types of depression can be understood. (E.g. due to the underlying

psychosis, or psychosis frequently co-occurring). In contrast, in our application we have presented new use. The examiner further brought prior art to our attention to which we are giving our answer at various parts in this reply. So, the expression of "known to be useful" is likely to be misleading out of context. In fact, we have shown the opposite, the strong teaching away from our method [that even continued after our applications. (Please also see Reply-14, and Secondary factors, after our boxed "line-by-line" reply).

In regards to the examiner's highlighted (bold) comments: please note, that with the introduction of newer atypical antipsychotics (for the treatment of schizophrenia), no studies were required to the same extent that the examiner demands from us. These atypical antipsychotics have still not been compared with each and all traditional (typical) antipsychotics regarding their efficacy, nor were required any and all antipsychotics be tried out in combination with any and all antidepressants for the use for example of psychotic depression or depression in schizophrenia. Please note, that for FDA approval, the atypical antipsychotics have not been required to be tested for psychosis, and their FDA approval was based on patients with schizophrenia, but that was sufficient for the skilled in the art to apply it to the clinical setting. So demanding enablement disregarding of how the clinicians can use a medication or combination off label, (see explanation in the next paragraph of this box) or disregarding that **enablement** does not need to be for a method involving **any antidepressant and any antipsychotic,** in our case, just as it has not been a requirement for major pharmaceutical companies. (Please see also Reply-10). The facts had also been left out that numerous combination of antidepressants and antipsychotics had been in use for long (for other reasons) as we had pointed out in our utility.
Now, it is well known for those skilled in the art (psychiatrists, clinicians), that once a medication is approved by the FDA for any reason or indication, the doctors can use that medication **off label**. That means, that no further large studies, toxicological and other animal studies are required for that medication to be used for another indication, or in combination with another FDA approved drug. To use a medication off label, (in non FDA approved dose or indication), the clinicians can rely on case studies, or appropriate guidance from others. We feel, that the description in our patent application(s) gave ample of guidance, and placed the invention in the hand of the skilled in the art, so that without undue experimentation he or she can use the invention relying on that guidance. For off label use of a medication or combination thereof, the clinician also need to go over the risk/benefit/alternatives analysis, and as we shall point out we have also given guidance in this regard. The off label use in our invention is even easier, as this class of medications even had been used in combination for psychotic depression or in schizophrenia for example, so any potential drug-drug interaction is know to the skilled in the art. Therefore, the examiner incorrectly states, that there would need to have an extensive animal and human trial with undue burden to use our invention, disregarding the fact of how off label medications are used, and disregarding our detailed, and very specific guidance that we have been giving.

Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcome even in patients not suffering from psychotic symptoms.

Reply-3: The examiner does not state anything negative with this on our application.

The state of the prior art: *Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art.* The antipsychotic drugs known to be useful in this method are of the newer, atypical variety. No general theory has been provided which would explain the usefulness of atypical antipsychotic drugs for treating depression, or determining which specific drugs are the most likely to be useful. Although a number of drug combinations have been tested and found to be useful, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods.

Reply-4: As in the first part of Reply-2, the italic highlighted part of the examiner's comment can be misleading for the same reason. Please see our correction in this regard there under Reply-2.
The examiner's statement (that we underlined) are potential for misunderstanding. It is true, that for other use than our invention a number of combinations were tested, but at the time of our application for the purpose of our invention (new use) none of these combinations were tested. If they were there would be a prior art against our invention. If the examiner intended to say that the use of the typical antipsychotics were not used in combination for (other use) like psychotic depression, that is incorrect. Dopamine system stabilizers such as aripiprazole have not been tested to my knowledge at the time of our invention for psychotic depression in combination with antidepressants, but I'm sure that by now that medication was used clinically either in a patient with schizophrenia and depression (with an antidepressant) or for psychotic depression.
The potential conflict and defense against the Tollefson, Faour, and Chappell references are discussed in our reply elsewhere. (Please see Reply-22, 23, 25, and 26,).
If the examiner meant to imply that undue experimentation would be necessary as these medication combinations were not tested yet for the new use of our invention, than the off label rule, and Reply-2, above would apply. See also Section on Enabling at the end of the reply.

The relative skill of those in the art: The relative skill of those in the art is high.

Reply-5: The examiner does not state anything negative with this on our application.

The predictability or unpredictability of the art: **In the absence of any general theory explaining the action of atypical antipsychotic** drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because the terms antidepressant and antipsychotic both encompass a large number of drugs of varying structures and methods of action, and because *antipsychotic drugs differ significantly from each other* as disclosed in Applicant's specification, (p. 13, lines 11-15) *no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally.* Thus the **effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of**

depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable.

Reply-6: The examiner states, that no general theory has been provided, but we have been giving guidance to enable the use of our invention. (Actually, in the provisional application we have given a theory; or better yet reasons of why the (atypical) antipsychotic medications (either alone or in combination with antidepressants) may target and be useful for the treatment and prevention of depression and suicide. These reasons were based on our synthesis of multiple source of information and on our conclusions that others failed to make. We have included these for our reply in Appendix A, B, and C. Pages 76-93.)
As regards to the following underlined segment this again is an incorrect conclusion as it is applied against enabling, - as we have given guidance, and pointed out that the off label use of these medication does not require undue experimentation on the part of the psychiatrist. (See Reply-2, for more details).
Than the examiner states: "because *antipsychotic drugs differ significantly from each other* as disclosed ... *no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally.*" However, the examiner had left out our guidance pointing to that our invention is enabling. (Please see also Reply-8 and 20).
The examiner's statement of: "**effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable**", would contradict to his other statements that our invention would be anticipated (obvious) from prior art. Here the examiner also contradicts his own statement he made above the box Reply-12: "the specification, while being enabling for a method of treating depression and associated conditions". See also Section on Enabling at the end of the reply.

The Breadth of the claims: The claimed invention encompasses combination therapies of any antidepressant with any antipsychotic. In particular, it encompasses combinations in which the antipsychotic is a typical or an atypical antipsychotic, or a dopamine system stabilizer.

Reply-7: The examiner does not state anything negative with this on our application.

The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17)

Reply-8: It is true that two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method, but that "squeezed in" a number of other potential case studies and possibilities into two patients. Furthermore, the body of our application(s) have provided more than adequate guidance to the skilled in the art. (Please see also Reply-20).
Our guidance should not need to prove any and all questions that a clinician may face, but to enable the clinician (one skilled in the art) to practice our invention without undue experimentation, and we have met this requirement with the ease of how off label use of

medications can be put to work.
See also Section on Enabling at the end of the reply.

The presence or absence of working examples: No working examples of the claimed therapeutic methods is provided by Applicant.
Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as antidepressant/antipsychotic combination therapy. See MPEP 2164.

Reply-9: The examiner errs with his conclusion as we had shown for example under Reply-2 (off label use), Reply-6, 8, and 20, (Zyprexa®/olanzapine); that we had shown that our guidance is adequate, and shifts unpredictability to predictability, and enables the skilled in the art to practice our invention.
We also have to disagree on this field being an undeveloped art, and state the opposite, that this is a crowded art. The use of antidepressant/antipsychotics for other indications had been used for long (e.g. for psychotic depression), there are numerous antidepressants on the market, so it is a crowded art. As the FDA director's statement – and other secondary factors show our invention is also an answer for a long felt unsolved need. (Please see discussion on secondary factors after our boxed "line-by-line" reply).

Please note that the current Government sponsored study (CATIE) to compare atypical antipsychotics with one single typical antipsychotic cost $40 Million, [and the data may be useless due to poor design] which is out of the scope of this independent inventor. (Please also note that Einstein's theory of relativity was proven with the development of atomic clocks well after his death and – would his invention otherwise be patentable – no-one argues that would have deserved a patent.) But back to the cost of these studies: When this applicant applied for government grant for a method that was already conceived by him, (on better ways to treat addiction as addict persons are not motivated to engage in therapy), he was rejected with a letter that the government can only sponsor ideas that had not been invented yet, and if I had already invented [but not disclosed], they encouraged me of just publishing it. (If necessary, a copy of this letter can be located and enclosed). The applicant has other responsibilities to win bread for a living, and does not have an asset to that degree to sponsor studies. However, all these may be beside the point. We have shown that the invention can be used off label, without undue experimentation, without such large studies. We have also shown that the skilled in the art does not have to get all his questions answered, but to enable him for the use of the invention (for which no more scrutiny than for a drug company should be expected). If for any reason a drug company would want to use this invention for the purpose of getting FDA approval, (and with that as a fringe benefit) getting an extension for that drug company's existing patent, than necessary large studies can be performed as much as that is required for such a purpose. However, to enable the skilled in the art to practice the invention, we had fulfilled the requirement giving adequate guidance for being enabling.
[Please also see under Reply-6;]

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants and

antipsychotics useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, *many different combinations would need to be tested* in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method. These **experiments would be repeated for each combination in animal models** of depression, *cognitive distortions*, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that **evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult** than evaluating a therapy for a nonpsychological condition such as cancer or arthritis.

Animal experiments include, along with the actual administration of the potential pharmaceutical compound and collection and analysis of data, **additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals** after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these **animal experiments would need to be repeated many times, and involve the maintenance, killing, and disposal of many experimental animals**, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro.

The scale of animal testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention.

Reply-10: The examiner again draws conclusion on that the art is unpredictable, yet we have shown evidence to the contrary with the guidance we had given.

The examiner also disregards the facts of how once FDA approved, the medications can be used **off label**. [see Reply-2]

Therefore no animal experiments are needed. Medications listed as potential use that are currently in drug development, (and patented as either antidepressants or antipsychotics by other patent holders) would need to go through the necessary steps that is required by regulatory agencies for approval. However, the statement of the examiner is incorrect even in this regard, since if what he states would be correct, no medications would ever be patented, or approved.

The main point is that we have enabled the clinicians to practice our invention. Clinicians can put our invention to work right away with our guidance and with the ease of "off label" use for the already FDA approved medications (for which by the way ample of experience is available even as regards to drug-drug interaction, since these medications in combination had been used for other purposes than our invention). We do not need to prove all possible combinations, just like the under Reply-20, for olanzapine in order of being patented, it was not required to have long term effect and data on maintenance therapy.

patients. [redacted] there is no body of evidence available to answer the question of how long the patient treated with olanzapine should remain on it, [redacted] (Yet, this antipsychotic would not be useful for schizophrenia if it could not be used long term for years).

It is within the skills of one skilled in the art to realize of what medications had been already approved, hence adjust to the currently available medications, or as they will become

available.
The same principles above would apply not only for the treatment of depression, but cognitive distortion, and smoking cessation. Therefore, our invention is enabling, and puts the method in the hand of the skilled in the art.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but **compensation for its successful conclusion.**" And "patent protection is granted in return for an **enabling disclosure of an invention**, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention **with every possible antidepressant and antipsychotic**.

Reply-11: We agree of the above, that a patent is a **compensation for its successful conclusion,** -and we have provided a successful conclusion that others (like the FDA directors) has failed to realize even in the intense media attention on the topic of our invention. As regards to patent protection is granted in return for an **enabling disclosure of an invention,** we could not agree more. The examiner had alleged, that Tollefson and other prior art anticipated our invention, and we had shown the opposite. (Please see under Reply-22-26,) If you compare the disclosure of Tollefson, that the examiner had claimed would make ours "obvious" from the Tollefson patent, (no disclosure of any sorts for new use conflicting with ours was given in Tollefson's reference and, no discussion of risk/benefit over alternatives was given), and compare this with our disclosure, that is extensive, and details risk/benefit analysis in light of available alternatives, - and if you also compare all this with our Reply-20, (olanzapine long term use example, where again no guidance were given), than you can see that we have provided extensive guidance, even on how long to use the combination for various purposes. (Please also see amendment to the specifications taken from the provisional application).
This shows that in fact our invention is enabling and meets the requirements that Genentech, 108 F.3d at 1366, sates, the Wands factors.
See also Section on Enabling at the end of the reply.
As regards to the examiner asking us "to provide information sufficient to practice the claimed invention with every possible antidepressant and antipsychotic", we have to refer to Reply-2 above. In addition as stated under Reply-10: "We do not need to prove all possible combinations, just like the under Reply-20, for olanzapine in order of being patented, it was not required to have long term effect and data on maintenance therapy."
Our guidance has enabled the skilled in the art to practice the invention without undue experimentation.

Claims 42, 48, 53, and 54 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression and associated conditions, **does not reasonably provide enablement for preventing depression or the progression or relapse thereof.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the

invention commensurate in scope with these claims.

Reply-12: The examiner makes this general statement in the light of the Wands factors that follows.
The examiner stated that the specification: **does not reasonably provide enablement for preventing depression or the progression or relapse thereof.**
We have to disagree with this statement as we have provided enablement in our applications; we have been giving detailed guidance to the skilled in the art of how to use our invention. We have been even giving detailed guidance of how long to use the combination therapy. We have even given hypothetical case examples to illustrate the use of our invention. In addition, the skilled in the art with our guidance and with the knowledge available at the time of invention on the prevention of depression would have been able to use our method without undue experimentation. We have also given example of the ease of off label use of medications before.

In our utility and provisional applications we have specifically given guidance:

I); Utility Page 10 lines 30-32, page 11 lines 1-3: ...In addition, depression may emerge during treatment with antidepressants in non-depressed patients (Fux, M. et al 1993, Fava, G.A. 2003,), and antidepressants may have a paradoxical effect and may be sensitizing patients to depression or relapse. (DiMascio, A. et al 1968, Fava, G.A. 2003). The combination treatment may also be protective for this phenomenon. The combination treatment may help avoiding the worsening of depression caused by the antidepressants.

II); Utility Page 17, lines 10-24:
In both of the above patients the antipsychotic is discontinued in two months. Although some patients may show a relapse with the discontinuation of the atypical antipsychotic; the patients in both of these hypothetical cases continue to do well just on the antidepressant at the 10 months follow up. In the first patient the depressive symptoms return and the increase of fluoxetine is providing only temporary relief. At the 12 months follow up he is feeling very depressed again on 50mg of fluoxetine. Pharmaceutical tolerance to fluoxetine is assumed, and risperidone is restarted at 1mg q d with dramatic improvement within one week. Two months later this male patient notices galactorhoea (milking of the breast) that is found due to the prolactin elevation from risperidone. Risperidone is discontinued, but within a week his depressive symptoms return. He is than started on 50mg of quetiapine a day, and does well. Although the patient has a strong family history of recurrent major depression (despite of continuous SSRI intake in these relatives), he continues to do well on fluoxetine-quetiapine combination, and his depressive relapses are avoided at the 5 year follow up.

III); In addition in our provisional at page 59 (last paragraph), = On PTO is 0286:
The issue of how long one should take an antidepressant needs to be discussed with the patient. There are only general guidelines for this. The "rule of thumb" varies by how many times the patient relapsed (possibly also taking into account the family history), the patient's age, and (with the newer safe antidepressants) if the patient wants to risk a relapse. These guidelines are known to the clinicians.

IV); provisional at page 60; second paragraph lines 6-14, = On PTO is 0288 line 5-7:

For psychotic depression some recommended using the neuroleptic for one year as the

depressive relapse is high otherwise. (Keck, P.E. et al. 2000 (a),). ...

In addition we specifically mentioned that the two medication in combination would potentiate each other.

The examiner had already acknowledged the novelty of our invention (in the box above Reply-14). There is a big fight within the pharmaceutical companies over a multibillion dollar antidepressant market (that is expected to reach $20.5 Billion by 2007, [see "enclosure on antidepressant market (a-c)"]. There is at least $100-200 Million per every percentage point gain. The fight for the antipsychotic market is similarly vigorous. [see "enclosure on antipsychotic market"]. As it can bee seen from the antidepressant advertisement (see reference under Reply-19), that focuses on the prevention of depression (showing why their drug is proven "better"), the drug companies are using every possible "edge" to get ahead of the market, and be competitive. (This also shows that the depression prevention is a crowded art.) Yet as secondary factor showing unobviousness of our invention, even more than four (4) years after our application, others with major interests are still not teaching our method. Now, it is true, that we made the conclusion and were teaching (we did, but not others) that antipsychotics (preferably with combination of antidepressants) may be used for treatment of cognitive distortion.

Now, it is also known that cognitive therapy targets cognitive distortions, but the two things (medication or "talking therapy") are not the same. That would not make our method obvious (aside, that the risk/benefit/alternative analysis must also be used). One is a solution with medication (antipsychotic or with antidepressant), the other is a solution with talking therapy.

In the first box within this box, our quotation under *IV);* on the high relapse rate points out that it is well known in the art (specifically for the psychotic disorders), that the discontinuation of the medication would cause a relapse. Yet as we have shown with Zyprexa®/olanzapine under Reply-20, no evidence was required by the PTO and FDA for long term (years of) maintenance therapy.

So, in summary, we have shown that we have a novel technique in this regard (that the examiner have acknowledged himself (in the box above Reply-14), and as the secondary factors also show, this method is unobvious. Furthermore, our guidance is enabling.

(In addition, further discussion of enablement for preventing depression or the progression or relapse can be found in Appendix B (relying on Appendix A), as well as in paragraph 12 of Appendix C, Page 76, and 86).

Nature of the invention: The claimed invention is drawn to a method of treating or preventing depression, relapse of depression, or various complications thereof, by administering to a patient in need thereof a combination of an antidepressant and an antipsychotic.

Reply-13: The examiner does not state anything negative with this on our application.

The state of the prior art: *Combination therapy with antidepressants and atypical*

antipsychotic drugs has been taught in the prior art. The antipsychotic drugs known to be useful in this method are of the newer, atypical variety. No general theory has been provided which would explain the usefulness of atypical antipsychotic drugs for treating depression, or determining which specific drugs are the most likely to be useful. **The prior art does not teach a method of preventing recurrence or relapse of depression through antidepressant/antipsychotic combination therapy.** As evidenced by the existence of treatment-resistant cases of depression, *no therapy is 100% effective at preventing the progression, recurrence, or relapse of depression.*
Similarly, treatments for smoking cessation and nicotine addiction generally have a high rate of failure and relapse. *No treatment has been found that can perfectly prevent relapse of smokers attempting to quit.* A smoker who is not exceptionally committed to quitting will eventually start smoking again regardless of which drugs are administered.

Reply-14: The examiner starts with "*Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art.*" This is only partially true, as we have explained in detail, that combination therapy have not been taught for the purpose of our invention (and even Tollefson, Faour, and Chappell references had failed to provide any guidance that could even remotely suggest that they were in possession of our invention). [We have discussed this above, e.g. Reply-2; and Reply-4; and please also see Reply-22-26,]

The examiner states, that No general theory has been provided, but we have been giving guidance to enable the use of our invention.

The examiner's next statement of "**The prior art does not teach a method of preventing recurrence or relapse of depression through antidepressant/antipsychotic combination therapy.**" acknowledges the novelty of our invention. Secondary factors also support unobviousness, that this is in a competitive market and players with major interests to gain marketshare have still not been using or teaching our method over four years after our application.

The examiner follows that "*no therapy is 100% effective at preventing the progression, recurrence, or relapse of depression.*" This is true, but cannot be brought against us, neither as regards of the patentability nor of the usefulness of the method. Prenatal vitamins are used (and approved) for the prevention of cleft palate in the newborn, prevention does not need to be 100% to be effective and useful. Aspirin is used for prevention of heart attack yet heart attacks still occur every single day as an "epidemic". Preventive medicine as such is not 100% effective. Significant difference (an improvement over previous methods) that can be expected is of great value in any medical treatment.
Please also note of what we said under Reply-8 for olanzapine. It is expected that for the treatment of schizophrenia a long term medication management is required, (it was already known for typical antipsychotics that discontinuation of the therapy leads to relapse) yet FDA and the PTO did not require years of long term studies for maintenance therapy for olanzapine. Relying on the skill of one skilled in the art with the guidance they provided was sufficient to use olanzapine for the purpose intended, without undue experimentation. The same enabling can be said for our methods.

The examiner last statement in this box "*No treatment has been found that can perfectly prevent relapse of smokers attempting to quit.*" *Is correct.* We have stated the same in **page**

5 of our Utility. This shows that there is still a demand of a long felt unsolved need, and therefore additional treatment methods (possibly even with combination of other already approved treatments) can be a significant contribution to the field. Our guidance was enabling though for the skilled in the art, and there is no statement to the contrary by the examiner in this box.

The relative skill of those in the art: The relative skill of those in the art is high.

Reply-15: The examiner does not state anything negative with this on our application.

The predictability or unpredictability of the art: In the absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because the terms antidepressant and antipsychotic both encompass *a large number of drugs of varying structures and methods of action, and because antipsychotic drugs differ significantly from each other* as disclosed in Applicant's specification, (p. 13, lines 11-15) *no one example of group of related examples can be predictive* for demonstrating the effectiveness of antidepressants combined with antipsychotics generally.
Furthermore, **depression denotes an observed symptom rather than an underlying condition.** Different cases of depression differ from one another to the extent that a skilled practitioner must determine the best course of therapy empirically by administering one drug after another to a patient in order to find one which elicits a positive response. Thus it is highly unlikely that it is possible **in all cases of depression to prevent progression, recurrence, or relapse with 100% certainty**. Thus the prevention of progression, recurrence or relapse of depression is highly **unpredictable**.
In the case of cognitive distortions, smoking cessation, and nicotine addiction, the art is even more unpredictable. Both cognitive distortions and addictions have a **strong psychological component, and the motivation** of a patient to change is an essential factor in determining treatment outcome, and **one which cannot be improved by any drug therapy**. In particular, smoking cessation is rather difficult even with the aid of drug therapy, and most smokers who attempt to quit eventually suffer a relapse and start smoking again. Thus the treatment outcome in the treatment of cognitive distortions and nicotine addiction is highly unpredictable.

Reply-16: In regard of the examiner's statement of "it is not possible to predict the efficacy of any particular antipsychotic", our guidance that we provided shifts our method to the predictability, and that we have enabled the skilled in he art to practice our invention without undue experimentation.
As regards to "any particular antipsychotic" we have discussed that under Reply-2 and 11.

With the data we have provided on the neuronal changes, and volume changes in hippocampus and prefrontal cortex of the depressed, the examiner's statement of: "**depression denotes an observed symptom rather than an underlying condition.**" is not

quite correct. (Please also see Appendix C). We have shown that even psychological effects alone would result in neuronal changes (through neuroplasticity), [and that in turn can have an effect in changing gene-expression]. Our synthesis is exemplary in attempting bringing psychological, pharmacological, neuronal, [and even potential gene-expression] changes together. This is especially true if you compare the TV and media advertisement (e.g. by Pfizer drug company, in providing explanation for depression as a missing neurotransmitter that need to be replaced by a medication). So our guidance is really extensive, and even goes beyond what would be minimally sufficient to one skilled in the art to practice our invention.

The examiner's following statement is incorrect: Different cases of depression differ from one another to the extent that a skilled practitioner must determine the best course of therapy empirically by administering one drug after another to a patient in order to find one which elicits a positive response. This would suggest that the practitioner would shoot in the dark until finding the working ingredient. In most cases this is incorrect. In case of TRD there is more trial and error, but the clinician may add adjunct medications. The following conclusion by the examiner, **"in all cases of depression to prevent progression, recurrence, or relapse with 100% certainty"** is answered again as in Reply-14.

The examiner than supports his conclusion that for "cognitive distortions, smoking cessation, and nicotine addiction, the art is even more unpredictable," based upon his assumption that "both cognitive distortions and addictions have a **strong psychological component, and the motivation** of a patient to change is an essential factor in determining treatment outcome, and **one which cannot be improved by any drug therapy**."
(Please also see Appendix C). We have shown that even psychological effects alone would result in neuronal changes (through neuroplasticity), [and that in turn can have an effect in changing gene-expression]. Our synthesis is exemplary in attempting bringing psychological, pharmacological, neuronal, [and even potential gene-expression] changes together. No-one else had done that synthesis before, in regards to depression and clinical neuroplasticity. **With this we have proven the opposite:** In addition, it was shown (please also see reference to that in our applications) that nicotine replacement drug therapy is highly inefficient, and I can concur with the examiner on the high rate of relapse, specifically as it is also known for most smokers – they relapse long after they are withdrawn from the nicotine. So to search for an answer, one should consider the thinking pattern of the smokers predisposing them to relapse, so targeting cognitive distortions (e.g. "I won't get cancer, or everybody needs of dying of something") either by cognitive therapy or pharmacotherapy or both can add to the sequel of the currently available techniques. This underlines the importance and a need for a new method like ours. Never the less our technique and guidance is enabling the skilled in the art on how to use the invention.

The Breadth of the claims: The claimed invention encompasses combination therapies of any antidepressant with any antipsychotic. In particular, it encompasses combinations in which the antipsychotic is a typical or an atypical antipsychotic, or a dopamine system stabilizer. **Prevention is interpreted to mean the complete, 100% effective elimination of any progression, recurrence, or relapse of the disease while the patient is maintained on the therapy.**

Reply-17: In the first part of this box the examiner does not state anything negative with this

on our application. (Please also note the amendment of our claims based on our applications.)
The bold section from the examiner is incorrect and a reply was given to that effect under Reply-14.

The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17) No reason is given to suppose that he claimed methods are **perfectly** effective at preventing progression, recurrence, or relapse of any instance of major depressive disorder,

Reply-18: Actually much more guidance was given than the two hypothetical examples in the body of the utility, and in the provisional, as it had been pointed out above. In addition the two hypothetical cases had "squeezed in" many more potential case examples within the two cases. For the underlined and bold part of the examiner's statement regarding it's incorrectness we have answered under Reply-14; Reply-16, and Reply-17.

The presence or absence of working examples: No working examples of the claimed therapeutic methods is provided by Applicant.
Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

Reply-19: Our guidance that we provided shifts our method to the predictability, and that we have enabled the skilled in he art to practice our invention without undue experimentation. We have also stated that the area of depression treatment is a crowded art. It is a multibillion dollar a year market, a very competitive business for the pharmaceutical companies (see enclosures a-c).
Since our applications, there are more publications on the prevention of depression (again not conflicting with our invention). [Please see please see Reply-12 and enclosure - Effexor-XR advertisement in Archives of General Psychiatry August 2006, 63: starting after page 888 –copy enclosed, and Wilson KCM et al, Br J Psychiatry 2003 182, 492-497, and Reynolds CF N Engl J Med 2006; 354:1130-8. copies attached]

Under Reply-9 we have discussed the issue of working examples.
[Please also refer back to Reply-12,]

All this shifts the argument toward the predictability with our guidance. Please also see Appendix B at Page 83, on enablement of preventing depression (page).

The quantity of experimentation necessary: **The short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness** for prevention of disease. Because **no guidance** is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so **without first gathering information as to the long-term effectiveness of the therapy**. Furthermore, in order to prevent recurrence of depression, cognitive distortion, or nicotine addiction as described above, the claimed therapeutic method, which

comprises nothing more than administering a drug, **must be able to fully counteract the effects of genetics and psychology** in order to prevent the subject from **ever** becoming depressed, having distorted cognition, or smoking again, regardless of the subject's motivation, or any environmental stresses which may encourage the re-emergence of the subject's condition. **Such a method would represent a significant novel improvement beyond anything disclosed in the prior art** or in Applicant's disclosure, particularly in light of the high relapse rate for smokers attempting to quit. *In order to develop such a method* in the absence of any existing data, one skilled in the art, *in order to practice the invention, would undertake long-term human* ***or animal tests*** *in order to study the effectiveness of the claimed therapy for preventing recurrence or relapse after the initial recovery.* **Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished.** Human tests impose additional ethical and regulatory burdens.
Performing these studies with no guidance from Applicant or from the prior art is an undue amount of experimentation needed in order to practice the full range of the claimed invention.

Reply-20: For the first part of the examiner's statement on "**The short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness**" please see Reply-8 on risperidal.
"The PTO should expect no more scrutiny from an independent inventor than from a major pharmaceutical company: Please note for example the 2003 PDR for olanzapine, under Dosage and Administration – Maintenance Therapy: While this medication is patented and FDA approved, the PDR notes that "...no body of evidence available to answer the question of how long the schizophrenic patient treated with Zyprexa®/olanzapine should remain on it..." (Please see PDR cut out under Reply-10, and pertaining full copy from the PDR in the enclosure).

While for olanzapine the question was "**guarantee of its long-term usefulness**" without research data (showing that maintenance can be maintained for years) and that was still leading for PTO and FDA approval. Yet it was known that these medications would be used long term for the treatment of schizophrenia (to be precise long term in case of schizophrenia means indefinitely, for years or decades, otherwise the relapse would be predictably high). In our case the use is for prevention of disease. However, in contrast to the PDR and the olanzapine example, we have provided guidance even detailing of how long to use the medication(s). [see Reply-12);]. So the examiner's assumption that **no guidance** was given is incorrect.

"Our guidance should not need to prove any and all questions that a clinician may face, but to enable the clinician (one skilled in the art) to practice our invention without undue experimentation, and we have met this requirement with the ease of how off label use of medications can be put to work."

The following section is of particular interest, since we have shown exactly what the

examiner was stating that it is missing as an explanation: "in order to prevent recurrence of depression, ... the claimed therapeutic method, which comprises nothing more than administering a drug, **must be able to fully counteract the effects of genetics and psychology** in order to prevent the subject from **ever** becoming depressed, having distorted cognition, or smoking again, regardless of the subject's motivation, or any environmental stresses which may encourage the re-emergence of the subject's condition." Apart that "ever" becoming depressed or that under "any" stress (or any condition) is not a requirement for patentability (no 100% effect is required) - as we have highlighted under Reply-14; - **we have shown exactly of what the examiner is asking for**. (Please see: Reply-16 and also Appendix C). **So in fact we have shown that the examiner's statement of: "Such a method would represent a significant novel improvement beyond anything disclosed in the prior art" is indeed correct.**

The high relapse rate for smokers had been addressed under Reply-14.

The issue of *"in order to practice the invention, would undertake long-term human **or** animal tests"* **is incorrect,** based on our discussion of the **off label use** once adequate guidance was given, and based on Reply-2 (off label use), this Reply-20 (requirement on olanzapine analogy), as well as based on Reply-10.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but **compensation for its successful conclusion.**" And "patent protection is granted in return **for an enabling disclosure of an invention**, not for vague intimations of general ideas that may or may not be workable."
Therefore, in view of the **Wands factors**, as discussed above, particularly the *lack of precedent in the art for prevention of relapse* and the lack of guidance from Applicant's disclosure, Applicants fail to provide information sufficient to practice the claimed invention for the prevention of regression, recurrence, or relapse of disease.

Reply-21: (Please also see Reply-11, and 12). We agree of the above, that a patent is a **compensation for its successful conclusion,** -and we have provided a successful conclusion that others (like the FDA directors [mentioned later under secondary factors]) has failed to realize even in the intense media attention on the topic of our invention. As regards to patent protection is granted in return for an **enabling disclosure of an invention,** we could not agree more.

Our disclosure, is extensive, - and again in comparison to the Reply-8, and 20, the olanzapine long term use example, where no guidance were given, we have provided guidance even on how long to use the combination for various purposes. (Please also see Amendments to the Specifications – Guidance 3, taken from the provisional application). Furthermore, we have provided a synthesis of depression treatment from the interaction of psychological, pharmacological, neuronal, and [even potential genetic expression,] as stated under Reply-12, 16, and 20.
All of the above and Appendix B give adequate guidance for the skilled in the art to apply our invention for:

Pasted from page 6 of utility: The present invention provides the following benefits: preventing disease progression/modifying the course of depression, delaying/preventing

relapse or recurrence of depression, preventing the development of delusional/psychotic depression, being protective/(and/or) remedying the development of tolerance toward the antidepressant, and a possibility for providing a neuroprotective effect. It may also provide a more effective treatment, increase the response rate to treatment, treat the residual symptoms of depression, prevent the antidepressant's paradoxical effect of sensitizing patients to depression and relapse, and prevent the worsening of depression caused by the antidepressants.

Claims 1-2, 4-6, 9, 11, 13, 14, 16-18, 20-22, 24-26, 28-30, 32-35, 37-38, 42, 48, 49, 51, 53, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Tollefson. (PCT international publication WO99/61027, included by applicant with PTO-1449) Tollefson discloses a method of treating depression by administering both a serotonin reuptake inhibitor and an atypical antipsychotic. While one embodiment of this invention is a method of treating treatment-resistant depression, another embodiment is a method of providing rapid onset treatment of depression to a patient, (p. 2, lines 10-13) which is drawn to cases **which have not demonstrated treatment resistance.** This method anticipates instant claims 1-4, 9, 11, 37, 42, 48, and 49. **Note that depression is interpreted as being a cognitive distortion with functional impairment and health hazards according to instant claim 3.** Specific atypical antipsychotic drugs which may be administered in this method are olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone. (p. 3) Specific serotonin reuptake inhibitors which may be used are fluoxitene, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, and sertaline, (p. 4, line 5 - p. 5, line 14) **anticipating instant claims** 5, 6, 14, 16-18, 20-22, 24-26, 28-30, 32-35. Specific preferred embodiments utilize drug combinations listed on p. 5, line 23 - p. 6, line 1. All of the drugs included in the invention may be administered orally, (p. 14, lines 19-22) anticipating instant claim 38.
The claimed invention is thus anticipated by Tollefson.

Reply-22: For defending against **Tollefson** reference (See also Reply-26):
The examiner states that Tollefson's use of the medication combination for rapid onset of action would anticipate our claim. However the fact had been left out, that the same author Tollefson have published that the time to respond to antidepressant fluoxetine [alone, not in combination] was noted at Week 1, which is within the same time frame that he is claiming in the patent application for "rapid onset of action". Therefore Tollefson cannot claim (and in the approved patent did not have any claim about that) that the combination use would be a rapid onset when he published that the monotherapy fluoxetine achieved about the same time frame for response. (Tollefson G.D. at al How long to onset of antidepressant action: a meta-analysis of patients treated with fluoxetine or placebo. International Clinical Psychopharmacology **1994**, 9:245-250. –copy is attached). Similarly, and in accordance with Tollefson's 1994 publication, research also showed that the rate of action of oral older tricyclic antidepressants were found to act early in the responders within the first week of treatment. (Katz M.M. The timing, specificity and clinical prediction of tricyclic drug effects in depression. Psychological Medicine **1987**, 17:297-309. – copy is attached). So one could not expose the patients to the risk of antipsychotics if antidepressant monotherapy would show comparable or the same "rapid onset of action". Therefore the conclusion of the

examiner on Tollefson reference anticipating our claims is incorrect. However, there are more arguments in support of the patentability of our application:

Tollefson indeed discloses a method of treating depression by administering both a serotonin reuptake inhibitor and an atypical antipsychotic for treating treatment-resistant depression (TRD).

Tollefson also discloses his finding of rapid onset treatment of depression to a patient, (p. 2, lines 10-13), (and in page 22 lines 16-17 discloses that the effect was evident within seven days). However, contrary to the examiner's statement no mention, hint or reference is given in their entire publication that this would be their finding on any patient which have not demonstrated treatment resistance. In the contrary, Under their Clinical Trials, they only disclose a study on patients with TRD (page 21 and 22). Again there is no mentioning of patients with non-TRD. So the examiner's statement in this regard is not supported. In regard of potential extrapolation of these results to non-TRD patients, in potentially anticipating our claims, one should be attentive to the guidelines of general practice (and the lack of guidelines to the opposite in the Tollefson reference). Namely, in order to avoid malpractice, one should analyze and discuss with the patient the risk/benefit/side effect and available alternatives with the patient (and document such a discussion in the patient chart). This subject is known in risk management courses as informed consent. (Failure to do so can result in a malpractice suite.)

Now, if another technique would be available (and was at the time of their filing as we shall show) which would only use a single antidepressant, therefore avoiding the added (and potentially serious and lethal side effects of the atypical antipsychotics), and the rapid onset would be comparable [or even as in this case much faster, achieving a result within seventy two (72) hours instead of within a week], than the skilled in the art, (and Tollefson) could not and would not want to use Tollefson's technique as initial treatment (or for the prevention of suicide in non-TRD patients) based on the rapid onset of action. Therefore Tollefson's technique cannot anticipate our claims.

It is also notable that Tollefson did not disclose any reference in regard of discussion of alternative rapid onset action antidepressants, or why if at all their methods would be better or worst, than the other methods. We specifically would like to draw attention to this fact (and also that they only included reference in regards to other augmentation strategies to TRD in page 2 (Other publications) in their final patent number US 6,960,577 B2). So Tollefson with the lack of disclosure on risk/benefit and alternative technique did not place the technique to the hand of the skilled in the art.

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).) (cited in page 200, Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003.)

Actually, there are a number of rapid onset of antidepressant actions that were known at the time of their filing, a list of reference is enclosed here:

There are many other rapid onset antidepressant methods that carry less side effect risks and may actually act sooner than the Tollefson reference **The intravenous high bolus dose imipramine (tricyclic antidepressant) in a double blind study relieved depression almost completely within 72 hours.** (Malhotra S et al Loading dose imipramine – new approach to pharmacotherapy of melancholic depression. J. Pschiat Res. **1996** 30(1):51-58, - copy is attached). This is much sooner than a response in the first week reported by Tollefson, and this other method does not carry the risk of diabetes, TD and potentially lethal NMS.

Rapid antidepressant effect was noted in a study of 8 subjects with MDD with a single dose of NMDA receptor antagonist ketamine (preclinical studies preceding this publication): Berman RM et al Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000; 47: 351-354.

We were also mentioning in our application (provisional): patent # WO 95/00154, June **1993**, for **SSRI-lithium administration for rapid onset antidepressant action.** – This also mentions that the use of lithium to an antidepressant in treatment resistant depression had been long recognized, and it has become standard clinical practice. **Their claim is for rapid onset of action.)**

In addition, please compare the Tollefson's lack of disclosure on risk benefit and other alternatives to our detailed analysis as provided in our applications:

Pasted from utility (page 14.)

There are other strategies that target a faster onset of antidepressant action, (Montgomery S.A. 1997, Blier, P. et al 1997, Garattini, S. 1997,) **and if these were equally effective on reducing the risk of suicide, they may be preferable due to their potentially less severe side effects.** Stimulants are known to have fast onset antidepressant action, and are also used in combination for TRD (Ayd, F. et al 1987). Antidepressants with noradrenergic-serotonergic synergism, (either as a single antidepressant possessing these qualities, or as two antidepressants combined) have shown more rapid onset than SSRIs. (Glenberg, A.J. 2000, Quitkin, F. M. et al 2001, Nelson, J.C. et al 1991). Augmentation strategies used for treatment resistant depression could also be considered for initial treatment. **However, the rapid onset antidepressant action is unlikely to give the same protection than the antidepressant-antipsychotic combination, and the risk of suicide is still present with the more rapid onset antidepressant strategies. Therefore the antidepressant-antipsychotic combination has a unique role in the prevention of suicide.** No other combinations have been used for initial therapy; they are used in treatment resistant depression only.

Pasted from provisional

[in other strategies mentioned] ...patient taking other medications as well, or by using other augmentation strategy by e.g. by combining more than one antidepressants, or by using other strategy like of pushing up the dose of the antidepressant aggressively. This later is usually not followed, unless there is a comorbid disorder (like an eating disorder) where usually higher dose of the antidepressant is required for adequate treatment.

Another rapid action antidepressant effect that we disclosed in the provisional application.

An antibiotic that had been used to treat tuberculosis, DCS (Seromycine) with a partial agonist character at the GLY site and with an NMDA antagonist-like effect (or mixed agonist/antagonist effect) had been shown to display prompt antidepressant effects (before the X-ray changes)...

Therefore as other "more rapid antidepressant action" alternatives are available with less serious side effect profile, Tollefson's method over other alternatives cannot be used as initial treatment. Since Tollefson did not disclosed sufficient (or any) teaching in this regard (or did not show that he was in the possession of our technique) it is incorrect that the examiner extrapolates his invention to our indication(s). **That is the examiner cannot claim that one skilled in the art would have disregarded the risk/benefit available alternative analysis, and would have jumped to use his technique over others (with less serious side effect) as an initial treatment for the prevention of suicide**. Tollefson (or Faour, and Chappell) does not discuss other fast (rapid) onset antidepressant techniques available in the prior art.

One skilled in the art (a psychiatrist) cannot conclude to start Tollefson's method as an initial treatment for the treatment of suicide or to start Tollefson's method on most everybody as initial treatment, first choice of treatment, making that initial treatment the new standard of care. For the same reason one skilled in the art could not conclude that Tollefson's method was for the prevention of the progression of the disease, for the prevention against the paradoxical effect of antidepressants for worsening depression or causing suicidal ideation or suicide, or for treating cognitive distortions or for smoking cessation, when he did not even mention these). In addition in our example we specifically stated: "**SI improved even before his depression went away", suggesting a different action against suicidality then the antidepressant effect.** Now, it is of special note, that while an inferior product can be patented, a drug that is harmful (see risk/benefit/side effect, available alternatives) cannot be patented, and Tollefson failed to show that analysis. Our analysis, with the supporting data shifted this combination for a new use (with a different low dose and other specifications). Our teaching has shifted the risk benefit analysis with a synthesis of a number of supportive information, and as we have specifically provided a guidance.

The examiner's statement for the definition of cognitive distortion and that he bases that on our claim 3, is incorrect: "Note that depression is interpreted as being a cognitive distortion with functional impairment and health hazards according to instant claim 3." Nothing in claim 3 mentions depression. We have given a definition of what cognitive distortion is at page 15 of our Utility:

The term "cognitive distortion" is used as it is understood in the art (Burns, D. 1980, Beck A, et al 1979, Beck, J. S, 1995, [p119.]), and may include overgeneralization, all or nothing (always-never) thinking, discounting positives or negatives, blaming and "labeling", assumptions and predictions, and emotional reasoning, all of which lead to "jumping to conclusions", without analysis of the facts.
Cognitive distortions may contribute to or worsen a number of illnesses like addictions, smoking, pathological gambling, impulse control disorders, anger, with consequent

relationship (marital, work etc) conflicts, major depression, anxiety disorders (e.g., generalized anxiety disorder, panic disorder, OCD, PTSD), personality disorders, obesity, eating disorders (e.g. anorexia nervosa, bulimia nervosa), or possibly even some childhood disorders like oppositional defiant disorder, and conduct disorder.

In addition, to show that cognitive distortion cannot be equaled to depression and that with suicide the following should be noted. [All of Consid: A)/1) to Consid: A)/3) was known in prior art]:

Consideration: A): Cognitive distortion or depression, as well as depression or suicide, is not the same and cannot be said that the two terms are equal or interchangeable. It cannot be said that change in one necessitates a change in the other. It cannot even be said that change in one would anticipate and predict the change in other when the stakes are as high as people's life.

In regard to pointing out that lifting of depression may not mean the elimination of suicide; or the other way around, that suicidality may be taken away when suffering and depression persists, one should note the following: [All these were known prior to our patent application(s)]:

> **Consid: A)/1):** Late Victor Frankle a well respected Viennese psychiatrist and a concentration camp survivor had published (in his books) and also presented on recorded video his teachings: This teaching included that in desperate condition (like in the concentration camp where peoples security, dignity and everything else was taken away), there was one thing that nobody could take away and that was what meaning they contributed to the events. (E.g.: that one day somebody a grandchild would need them, and therefore this meaning was giving them the spirit to live).
>
> He emphasized, that despair underlies suicide attempt, and that does not equal to suffering [added: or depression, or suffering seen in depression].
> He made the equation of:
>
> Despair (underlying SI) = suffering without meaning.
>
> He demonstrated with a patient (a doctor himself) who came to see him (depressed), as that patient could not overcome the loss of his wife. When a meaning was added (that is that this patient surviving his wife spared her of a terrible suffering, but that was done at a price of him surviving and morning her) that took the despair away. He said the patient was still suffering (but the meaning took away the despair).
>
> Victor Frankle was also teaching that in the **most depressing environment** like in the **concentration camps suicide was extremely rare**. (One could not imagine worst than that, a more depressing environment, where everything was taken away from people.)
>
> This points out that depression and desperation and suicidal feeling out of hopelessness or giving up on life does not need to strictly correlate with the depression. Therefore assuming that depression treatment equals with the taking

away one of the symptoms of the depression, the suicide risk, is incorrect. [See Victor Frankle: The Will to Meaning, published by Zeig, Tucker and Theisen ISBN#: 1-932462-54-6.]

Consid: A)/2): Recurrent Brief Depression (RBD) that lacks the 2 week requirement for MDD, had been researched before our applications.
It had been described that fluoxetine had the same rate (or no effect) on the recurrence rate than placebo. Fluoxetine neither raised, nor lowered the suicide attempt rate compaired with placebo [for RBD]. (Montgomery D.B. et al, Eur Arch Psychiatry Clin Neurosci **1994** 244 (4):211-5. – copy is attached).
The same article also concludes, that RBD has a different pharmacology than MDD.

It also had been shown that RBD was associated with higher percentage of previous suicide and death. Maier W et al, Eur Arch Psychiatry Clin Neurosci **1994** 244 (4): 196-204. – copy is attached).

Since the by definition the depression in RBD lasts for less than two (2) weeks, the examiner's statement **that lifting of depression would anticipate lifting of cognitive distortion or of suicide risk is therefore proven wrong**.

Consid: A)/3): The topic that **cognitive distortion does not necessarily correlate, or correlate strictly with depression** is further supported by what we see in Borderline Personality Disorder (BPD). In this condition we can see significant mood lability, depression, [even though BPD is not listed under mood disorder in the DSM-IV-TR]. BPD patients can display bright affect at one point of time, but still have significant proneness to cognitive distortion, that can return at any time particularly in response to stress.

.

So, anticipating our invention for the purpose of new use on cognitive distortion and anticipating it from Tollefson, Faour, and Chappell, references is incorrect.

Anticipating our invention for the purpose of prevention of suicide and anticipating it from Tollefson, Faour, and Chappell, references is also incorrect for the same reasons. **These are further supported by:**

There are no single predictors of SI and all scales cannot predict SI.

Pasted from Utility.
Predicting which patients will commit suicide is an impossible task, and there are no models of suicide risk assessment that had been empirically tested for reliability and validity.

The risk of cognitive distortion and suicide may still linger around.

We have stated in the application that the antidepressant antipsychotic combination has specific role in the prevention of relapse, prevention of suicide, and protecting against the paradoxical effect of antidepressant to worsen the depression. This specifically had been stated in our application, and in comparison no guidance of any sort had been provided by Tollefson or Faour, and Chappell.

Consid: A)/4): Furthermore, let me share my experience when

a) I was providing psychotherapy (used here as the lay term of "talking therapy") to a patient undergoing ECT (electroshock) treatment (and the patient was also suicidal). This by itself to the extent of therapy I was providing was unusual. (Usually patients getting ECT do not get intensive psychotherapy). It was notable that the patient had made progress with the talking therapy, her affect got brighter during the therapy, but "tired out" after the end of the hour (session), and resumed her cognitive distortion. So the question is not only of whether the cognitive distortions are lifted (or show improvement) with the treatment of depression, but for how long the relative lack of cognitive distortions can be maintained. Another question is whether in stressful situations (even short term) these cognitive distortions would return exposing the patient again to the risk of suicide or relapse. These should be kept in mind by the clinicians and argue against the examiner's conclusions when he said that the Tollefson reference would anticipate our invention or that the lifting of depression would lift the risk of suicide and eliminate the cognitive distortion, disregarding our specific teaching on the role of antipsychotics and on the combination therapy.

b) I was providing psychotherapy ("talking therapy") to a patient where – everything have failed beforehand; even ECT and brain surgery for depression (cingulotmy). I had seen him for initial therapy after he was years over of these failed treatments. The patient was severely depressed, on medications, but was relatively free of cognitive distortions. Psychotherapy was useful for this patient and not recovery, but significant improvement was noted for the period I saw the patient.

This illustrates that cognitive distortions may be modified, but basic beliefs, and return of cognitive distortions may still play a role of SI, and that cognitive distortion does not necessarily correlates with the depression.

a); This also illustrates, that cognitive distortions may be lifted temporarily with the treatment of depression, and it may return quickly. So the treatment of depression does not equal to taking away the cognitive distortions, nor does it mean that the tendency for cognitive distortions and the "global" thinking style of the depressed is taken away.

b); Severe depression may be present with the patient being relatively free of cognitive distortion. [Although statement a); above is still true].

So general statements (from the examiner) of equaling depression and cognitive distortions are incorrect.

Similarly, one cannot equal depression with SI.

Pasted from Utility page 11:
Suicidal thought is one of the depressive signs tested and need not to be present for the diagnosis of MDD. … depression is not the only psychiatric disorder leading to suicide.

As we could see from Consid: A)/1) from Victor Frankle's teaching and from Consid: A)/2) on RBD; Consid: A)/3) on BPD; [or even from Consid: A)/4)]; one cannot equal depression with SI, or with cognitive distortion. One cannot state that a change in one

would anticipate and predict the change in other, especially when the stakes are as high as people's life.

All of the above, as discussed before points out why the examiner's conclusions or the Tollefson reference cannot anticipate our invention.

In addition, on page 13 Tollefson reference gives "general outlines" and "some preferred dosages" for the antipsychotics, but they give an extremely wide range and not a low dose (or due to the wide range not specifically a low dose).

For Olanzapine from 0.25-100mg preferred 1-30mg or 1-25 mg/day
For clozapine 12,5-900mg preferred 150-450mg
For risperidone 0.25-16mg preferred 2-8mg
Sertindole 0.0001-1.0mh/kg/day (no preferred)
For quetiapine 1.0-40mg/kg/day which is in an 80 kg patient 80-320mg/day (no preferred dose was given),
For ziprazidone 5-500mg/day (preferred 50-100mg/day)

This shows no consistency for a low dose or preferred low dose, (or a concept that low dose would be preferred), as for olanzapine this range includes high dose (even when considering for the treatment of schizophrenia). In fact their preferred dose range for olanzapine –their own drug - includes a top range that is up to 33% higher than the FDA approved dose! For risperidone the preferred range is relatively still high and not a low dose.

The same wide (or relatively wide) dose range (and no consistency) can be said to their preferred ratios of olanzapine/fluoxetine by weight. (page 14 lines 10-16) and that is repeated in claim 9.

They fail to give guidance to the skilled in the art, by providing wide dose range, and later being even more hesitant and widening more these ranges (page 14 lines 36-37 and page 15 line 1-2), that the composition may be the entire dose of one compound (not specifying which) and the fraction of the other compound.
On page 15 lines15-16 they state about the amount of the compound that it "is best defined as the effective amount" … "which provides the desired dose to a patient in need of such treatment", but failing to specify that.

From page 17 on they give examples of formulations,
Olanzapine/fluoxetine:
25/20mg ; [**high dose for olanzapine**]
10/10mg (extrapolated to the usually minimum effective dose of fluoxetine would be: **20**/20**mg** [**high dose for olanzapine**])
Risperidone/duloxetine: **5**/10mg [**high dose for risperidone**],
Sertindole/dulozetine: 60/20mg,
Quetiapine/fluoxetine: 70/30mg;
Ziprasidone/duloxetine: 75/5mg [again extrapolated this is relatively high dose for ziprasidone],
Olanzapine/Sertraline: **20**/100mg [this is **high dose for olanzapine** as it is, but extrapolating to the usually minimally effective dose of sertraline would be **extremely high**

dose for olanzapine, 40/50mg];
Olanzapine/paroxatine: **20**/25mg [**high dose for olanzapine**];

So, contrary to our detailed instructions, the Tollefson reference does not show a concept, that low dose of atypical antipsychotic would be preferred for the purpose of their claims.

Secondary factors also apply here that we have mentioned above, and additional factors that we should bring up after our line-by-line reply.

Claims 1-2, 4-6, 9-11, 13-14, 37-38, 42, 48, 51, 53, and 54 are rejected under 35 U.S.C. 102(e) as being **anticipated by Faour** et al. (US patent application, 09/728276, Pub. No. 2001/0048943 Al, cited in PTO-1449) Faour et al. discloses, "a method of treating depression, anxiety, and/or psychosis in a mammal, the method comprising administering **an osmotic device** which provides a controlled release of VFX [Venlafaxine, a selective serotonin and norenepherin reuptake inhibitor] from its core and a rapid release of an anti-psychotic agent from an external coat," (p. 2, left column, paragraph 0020) anticipating instant claims 1-3, 9, 11, 13, 14, 37, 42, 48, 49, 51, 53, and 54. This osmotic device is meant for oral administration, anticipating instant claim 38. Various embodiments of the invention of Faour et al. include a number of atypical antipsychotic drugs, (p. 2, left column, paragraph 0022-0023) including those recited in instant claims 5, 6, and 10. The instant claims are thus anticipated by Faour et al.

Reply-23: For defending against **Faour** reference:

Faour reference is a delivery patent not a new use patent. Although they describe "a method of treating depression, anxiety, and/or psychosis ... comprising administering **an osmotic device** which provides a controlled release of VFX [Venlafaxine, a selective serotonin and norenepherin reuptake inhibitor] from its core and a rapid release of an anti-psychotic agent", but from their description it becomes evident that this delivery system was intended for the use known in the art: Under 0004 line 2-6 they state: "On occasion, a person suffering from depression or anxiety and psychosis will be prescribed an antidepressant agent and an anti-psychotic agent. Rather than administering of two different dosages, it would be useful in the art to have available a single dosage containing both an antidepressant and an antipsychotic." They do not disclose nor do they give guidance anywhere in their application that the use of their delivery system would be for depression (Major Depressive Disorder) without psychosis, or without TRD. No risk/benefit alternative analysis or any guidance is given of why anybody should deviate from the standard of care, or even that one should think of a new use in this regard. In fact they list depressive states with (prevalent) psychosis (under 0091) and psychotic disorders with depression under 0093. One skilled in the art [without specific guidance in the patent] would have used this generic term of depression to apply the patent of Faour, over what was already known in prior art, that is to use the combination (and delivery systems) like for the treatment of psychotic depression, depression in schizophrenia and psychosis, in manic-depressive (bipolar) disorder (with or without psychosis, in depression seen in Borderline Personality Disorder (BPD), or for TRD. The skilled in the art could not have used their method for something that was not adequately disclosed, or for which no guidance was given of any sort.

In addition as in their claim 7 they give a dose range for risperidone 5 to 10 mg a day, that is considered compared to ours a high dose and not a low dose antipsychotic. No consistency or guidance is shown for a low dose antipsychotic use, or that how the treatment of psychosis should be different from non-psychotic disorders. They give a wide range of antipsychotic doses, that is consistent with the treatment guidelines that was suggested for the treatment of schizophrenia, to start the dose low to minimize side effect and retain the patient in treatment.
This prior art reference does not give indication of initial treatment or to use their method as initial treatment on most everybody, changing the standard of care (and using risk/benefit alternatives analysis. Nor do this reference give indication for the prevention of suicide, prevention of the progression of the disease, treatment or prevention for the paradoxical effect of antidepressants worsening depression, or causing suicidal ideation, or for cognitive distortion, or smoking cessation (new use). In fact **in Faour, no disclosure is given of why the combination use would be of benefit** (for other than what was already known in the art).
The **Faour** reference cannot anticipate our claims.

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

Claims 3-6, 9, 49, 50, and 51 are rejected under 35 U.S.C. 102(a) as being anticipated by George et al. (Reference included with PTO-892) George et al. discloses a clinical trial of bupropion for smoking cessation among schizophrenic patients. (p. 54, right column, second paragraph, p. 56, left column, figure 1) As these subjects were also being administered antipsychotic drugs for their schizophrenia, the varying effects of typical vs. atypical antipsychotics was also observed. (p. 56, right column, figure 3) Subjects taking atypical antipsychotics, in this case clozapine, risperidone, and olanzapine, were notably more likely to successfully abstain from smoking. (p. 56, right column, last paragraph - p. 57 left column, first paragraph) Thus George et al. discloses a method of treating a patient undergoing nicotine withdrawal or smoking cessation comprising administering to said patient an effective amount of an antidepressant in combination with an antipsychotic drug. Therefore the disclosure of George et al. anticipates the claimed invention

Reply-24: **Our claim indeed needs to be amended (to reflect use in non-psychotic patients);** we thank the examiner to bringing this into our attention.
For defending against **George** reference:

George reference cannot be extrapolated from the treatment of smoking cessation in schizophrenia.
This data cannot be extrapolated to non-psychotic, as in psychosis the antipsychotics also help improving reality testing, the disorganized thought process and are targeting the

response to hallucinations – all important aspects of the treatment of the psychotic individual, but not the depressed. One skilled in the art would realize, that with the use of antipsychotics, (and with a more effective treatment with atypicals), the symptoms of schizophrenia would improve, the patient with schizophrenia would be able to focus more to instructions, and follow counseling guidelines as part of most smoking cessation process. The relative difference or trend between atypical and typical antipsychotic drugs, in the better smoking cessation rates are not surprising as the newer (atypical) antipsychotic medications had been found to be generally more efficient in improving schizophrenia and psychosis, especially in subscales like (behavioral) withdrawal of the schizophrenics and negative symptoms. So with the overall improvement of the thought process of the schizophrenic individual, the smoking cessation rate can be expected to be better than those patients not getting treatment (or not as effective treatment) for their thought disorder. This would be understood by those skilled in the art. In accordance with this nothing is mentioned in George reference that the use of (atypical) antipsychotic with other antidepressants (or with buproprion, Wellbutrin, marketed for smoking cessation as Zyban) should be also tried in the light of this study in the non-psychotic, non-schizophrenic individuals. With such a surprising finding they would have made such a comment (or if they would have not, an editorial comment would have followed with such a suggestion). So, George's reference necessitates to amend of our claims (to be precise and exclude schizophrenia, and psychosis that is treated on a chronic basis with antipsychotics), but does not preclude the patentability of our invention in this regard. George's reference cannot anticipate our invention.

Claims 1-2, 4, 7, 9, 11-15, 37, 38, 42, 48, and 51-54 are rejected under 35 U.S.C. 102(e) as being anticipated by **Chappell** et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, cited in PTO-892) Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier, anticipating instant claims 1-4, 7, 9, 37, 42, 48, and 49. (p. 1, left column, paragraph 0002) General types of antidepressants which may be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, anticipating instant claims 11-13. Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, anticipating instant claims 14 and 15. The compounds used in this invention may all be administered orally, anticipating instant claim 38. (p. 22, paragraphs 0460-0462) Chappell et al. thus anticipates the claimed invention.

Reply-25: For defending against **Chappell** reference:

Chappell's abandoned publication gives the impression that they use the term depression as a wide range definition that specifically include psychosis (under page 1; 0009 line 8-9) schizoaffective disorder depressed type. On the other hand nowhere in their specification they mention that Major Depressive Disorder without psychosis or without TRD should be also included in their method. This wide range definition is troublesome (just like an even wider definition like "psychiatric illnesses" or illnesses would be), without them giving disclosure, a guidance or reason. Under 0020 lines 7-10, they further give indication that their method may be used for TRD: "it is possible to treat depression... in patients for whom conventional antidepressant ... therapy might not be wholly successful".

One skilled in the art [without specific guidance in this abandoned publication] would have used this generic term of depression to apply the publication of Chappell, over what was already known in prior art. **The skilled in the art could not have used their method for something that was not adequately disclosed, or for which no guidance was given of any sort.**

This prior art reference does not give indication of initial treatment or to use their method as initial treatment on most everybody, changing the standard of care (and using risk/benefit alternatives analysis. Nor does this reference give indication or adequate disclosure for the prevention of suicide, prevention of the progression of the disease, treatment or prevention for the paradoxical effect of antidepressants worsening depression, or causing suicidal ideation, or for cognitive distortion, or smoking cessation (new use). In fact **in Chappell, no disclosure is given of why the combination use would be of benefit**.
The **Chappell** reference cannot anticipate our claims.

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

In addition, the **Chappell** reference is also vague and gives an extremely wide dose range for the antipsychotics "from about 0.05 to about 1500mg per day". (page 22, 0459 line 15). Elsewhere, they refer to "an appropriate dose regimen designed to obtain the benefits of the combination therapy" (page 22, 0459 lines 7-9).

Alternatively they are implying the use of dosage for (FDA approved) antipsychotics customary for the treatment of psychosis referring to the PDR. Now, for the clinician (one skilled in the art) it is also known that initially with the introduction of atypical antipsychotics it was recommended, to start the dosing of these medications low to avoid side effects, than increase the dose to the **target dose** of treating psychosis. (Target dose for psychosis in the 2003 PDR (under Dosage and Administration) is for quatiapine 300-400mg; (and in other studies 400-500mg appeared to be needed; [Goodnick PJ. Higher than Physician's Desk Reference (US) doses on atypical antipsychotics. Expert Opin Drug Saf 2005 4(4):653-668. – copy is attached], for risperidone 6mg (3mg BID –twice daily); for zyprexa (for schizophrenia is 10 mg a day – [and in the 2006 PDR for maintenance of bipolar disorder the PDR lists 20mg/day dose]); for ziprazidone no target dose is given they recommend initial daily dose of 20 mg BID (twice a day) adjusted up to 80 mg BID with citing clinical trials of 20-100mg BID; (However, Expert Opinion pointed out based on studies that for ziprazidone only 200mg a day had shown statistical superiority over placebo. [Goodnick PJ. Higher than Physician's Desk Reference (US) doses on atypical antipsychotics. Expert Opin Drug Saf 2005 4(4):653-668. – copy is attached]); the 2006 PDR for aripriprazole lists a target dose of 10 to 15 mg a day for schizophrenia and for bipolar disorder a starting dose of 30mg a day. – copy is attached).

The current view on the average dose of these atypical antipsychotics for the treatment of psychosis is higher than it was initially approved by the FDA. Expert Opinion have stated that "pharmaceutical companies have frequently targeted lowest possible doses for FDA approval" and that the use of antipsychotics at these lower dose may limit the benefit in treating psychosis. [exception is for risperidone (due to EPS side effect on higher doses)]. This is also exemplified by the critics over a $40 Million government sponsored study giving invalid results, as that study was comparing the atypical antipsychotics with a single typical, but they have used higher dose only for olanzapine (exceeding the FDA approved highest dose with 50% for that drug), but not for the others. So with the exception of the above mentioned atypical antipsychotic risperidone, currently in use in the USA, the view is that the target dose for effective treatment of schizophrenia of these medication is higher (in average) than initially it was submitted to the FDA, and as listed in the PDR.

References: [Goodnick PJ. Higher than Physician's Desk Reference (US) doses on atypical antipsychotics. Expert Opin Drug Saf 2005 4(4):653-668, Citrome L, et al Dosing of quetiapine in schizophrenia: how clinical practice differs from registration studies. J Clin Psychiatry 2005; 66:1512-1516, Davis J.M. et al, Dose response and dose equivalence of antipsychotics J of Clin Psychopharmacol 2004; 24:192-208, Pierre JM et al, High dose quetiapine in treatment refractory schizophrenia Schizophrenia Research 73 2005 373-375, Pajonk FGB, et al Rapid dose titration of qutiapine for the treatment of acute schizophrenia and acute mania: case series. Journal of psychopharmacology 20(1) 2006 119-124, Albrecht A et al, High dose of depot risperidone in a nonresponder schizophrenic patient. J of Clin Psychopharmacol 2004; 24: 673-4, Duggal HS et al High dose aripriprazole in treatment resistant schizophrenia. J Clin Psychiatry 67; 2006 674-5, Williams R et al Optimal dosing with risperidone: recommendations. J Clin Psychiatry 62; 2001; 282-289, Cutler A.J. et al The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia. CNS spectr 11:9 2006, 691-702,]

But let's go **back to our argument**: The dose range of Chappell specifically them referring to the PDR, (that gives a target dose) does not indicate that they meant to use a low dose antipsychotic.

In fact all of the cited prior art references specifically were not teaching that a low dose antipsychotics should be used for the treatment of depression in combination with an antidepressant. **On the other hand a specific dose range with advantage, a better result is patentable, even if there is a wider dose range known in prior art**. (...A critical ... range will be considered novel,...even though it's technically embraced by the prior art. Page 5/15 Pressman D Patent it Yourself, Nolo 2004). We specifically stated over and over the importance of a lower dose and that it has an advantage. Also we have given a new use technique not previously disclosed by Tollefson, Faour, and Chappell. So, low dose (along with new use) and the secondary factors discussed below specifically argue for the patentability of our (amended) claims, and the disclosure of our invention. (In addition we have also indicated reasons for initial treatment and other new use.)

However the main argument is as we said that the **Chappell** reference (or the other references) cannot anticipate our claims.

Claims 3, 36, 39, 41, 43, and 49 are rejected under 35 U.S.C. 103(a) as being **unpatentable over Tollefson.** (PCT international publication WO99/61027, included by applicant with PTO-1449) Tollefson discloses a method of treating depression by administering both a serotonin reuptake inhibitor and an atypical antipsychotic. While one embodiment of this invention is a method of treating treatment-resistant depression, **another embodiment is a method of providing rapid onset treatment of depression to a patient, (p. 2, lines 10-13) which is drawn to cases which have not demonstrated treatment resistance.** Specific atypical antipsychotic drugs which may be administered in this method are olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone. (p. 3) Specific serotonin reuptake inhibitors which may be used are fluoxitene, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, and sertaline, (p. 4, line 5 - p. 5, line 14) Recommended dosages are given on p. 13. Tollefson does not disclose a method in which the antipsychotic is administered according to the dosage levels disclosed in instant claim 36. Tollefson does not disclose a method of administering the claimed treatments as soon as possible , or a method wherein treatment is given for preventing suicide. Tollefson also does not explicitly disclose a method of treating cognitive distortions as defined by Applicant's specification on p. 15, lines 9-14.

It would have been **obvious** to one of ordinary skill in the art at the time of the invention to use **aripiprazole** as the atypical antipsychotic in the methods disclosed by Tollefson et al. It would have been obvious to one of ordinary skill in the art to administer the drugs in the methods of Tollefson et al. at the dosages describes in instant claim 36. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapeutic method of Tollefson to a patient as initial treatment as soon as possible, and to provide treatment in order to prevent suicide, as described in instant claims 39, 41, and 43, and to treat cognitive distortions according to instant claims 3 and 49. One of ordinary skill in the art would have been motivated to practice the therapeutic method in this way because Tollefson discloses that his method is useful for providing rapid onset treatment, and thus for providing immediate treatment for emergency cases where time is of the essence, such as those in which the subject is at serious risk of suicide. One of ordinary skill in the art would have been motivated to use the doses described in instant claim 36 because the **ranges disclosed in this claim overlap with those disclosed on p. 13 of Tollefson** et al. One of ordinary skill in the art would have been motivated to use the method for treating cognitive distortions because cognitive distortions as defined by Applicant are often associated with depression. One of ordinary skill in the art would **reasonably have expected success in using the dosages of instant claim 36 because these dosages overlap with those taught by Tollefson** et al. and because **adjusting dosages within the general range known in the prior art** is well within the level of ordinary skill in the art. *One of ordinary skill in the art would reasonably have expected success in administering treatment as soon as possible to prevent suicide because suicide is known to correlate strongly with depression, and because treating a subject for a serious condition as son as possible is a generally recognized practice in the art.* One of ordinary skill in the art would reasonably have expected success **in treating cognitive distortions because treating the associated depression would lead to improvement in the associated cognitive distortions.** Thus the invention taken as a whole is prima facie **obvious**.

Reply-26: For defending against **Tollefson** reference: (Please see also Reply-22).

Under Reply-22 we have given specific detailed answer under the examiner's incorrect conclusion (bold).
We have also discussed that Tollefson does not imply a low dose antipsychotic use, (which is in accordance with the examiner statement: "Tollefson does not disclose a method in which the antipsychotic is administered according to the dosage levels disclosed in instant claim 36". However, the examiner errs on concluding that "One of ordinary skill in the art would **reasonably have expected success in using the dosages of instant claim 36 because these dosages overlap with those taught by Tollefson** et al. and because **adjusting dosages within the general range known in the prior art** is well within the level of ordinary skill in the art." First of all, Tollefson gives a wide dose range. Second, the issue is not the adjustment of the dose, as this dose adjustment are not done for the same reason that one would do such an adjustment for the treatment of psychosis, and the rules or guidelines are different in these two disorders. In psychosis, you look for hallucination, and side effects. You also know the target dose (published in the PDR or in the literature). You lower the doses (within the target dose) only if there are side effects. This is known in the general skilled in the art. On the other hand we have specifically draw attention in our utility for the use of low dose antipsychotics (and even given a specific guidance for the dose range). We have also mentioned, (utility page 2 lines 6-9) that even some of the atypical antipsychotics can show depressogenic properties. So, using high dose of antipsychotics would create an undue experimentation (finding that the patient's depression may worsen, and to find this out may take more time than noticing the hallucination in psychotic). Without guidance on the need for a low dose antipsychotic the clinician may also get into unfamiliar territory and unexpected difficulties of not knowing the reason and of what to do if the patients' depression would get worse. The clinician would not know if needing to experiment with high dose antipsychotics (in order to find out the dose range) that if the worsening depression would be from the depressogenic effect of the antipsychotics (as we have mentioned in our utility page 2 lines 6-9), therefore needing to lower the dose, or if the patient was not responding to treatment and therefore would need change treatment strategies like giving ECT. In comparison, in the treatment of psychosis high doses of antipsychotics are usually effective, and the dose can be lowered to the target dose.

Depressive signs may change more slowly compared to the change in hallucination of psychotic (which is more noticeable). Finding by experimentation, that a low dose antipsychotic should be given when treating depression, therefore is not the same than what the general artisan would be used to. So the examiner's extrapolation is incorrect and misleading, as the dose would not need to be adjusted due to side effect, but because the lower dose range is specifically desirable. Thus it would have to lead to experimentation, and hurting some patients until the clinician would have realized that what dose range would be needed for the purpose of our invention.

Under Reply-22 we have given specifics of why it would not have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapeutic method of Tollefson to a patient as initial treatment as soon as possible, and to provide treatment in order to prevent suicide, disregarding the risk/benefit and available (more rapid onset)

alternatives with less serious side effect.
In addition, we have also noted in the Utility page 2, 3,:

"There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression". In general, the use of antipsychotic drugs was reserved for use in patients having psychotic symptoms. It was generally accepted that antipsychotic drugs used alone could not treat major depressive disorder. In fact, it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)

A later review summarized the opinion, that "while a 'true' antidepressant effect has been demonstrated for the tricyclic antidepressants, similar effects appear doubtful for the antipsychotic drugs." (Nelson, J.C., 1987).

A book chapter reviewing this topic from year 2001 makes the point that "the risk/benefit ratio in refractory patients lacking such features [as near-psychotic rumination or marked psychomotor agitation] generally does not favor [antipsychotic augmentation]". (Price, H. 2001,).

We have already mentioned and are going to discuss later in details the secondary factors (including about Tollefson) and the FDA teaching away. We will also note the Texas Algorithm and others as they were also teaching away even after the filing of our application. (See later under Secondary factors). So, the examiner's conclusion that our technique would have been obvious from the Tollefson reference is incorrect.

Aripriprazole is a partial agonist antagonist, and at the time of the invention there was limited data available on aripriprazol. It is correct that aripriprazole was tried for the treatment of schizophrenia. It was suggested that this partial agonist/antagonist property (being dopamine system stabilizer) would put aripriprazole into a new class of drugs. So the examiner's conclusion is probably not true that at the time of our invention the average artisan would have wanted to substitute an atypical antipsychotic with aripriprazole for the purpose of Tollefson's technique. We should look for evidence that would suggest that indeed it was correct. There is no evidence suggesting that prior art would have anticipated what the examiner claims, and while drug companies would want to secure new indications and file for patents (they have failed to do so). However this point may be insignificant, as we have shown, that the examiner other statements of our method being anticipated by Tollefson had been strongly opposed both with factual data and with secondary factors presented later.

In Reply-22 we have also discussed under **Consideration: A):** that Cognitive distortion or depression, as well as depression or suicide, is not the same and cannot be said that the two terms are equal or interchangeable. These provide evidence that **"in treating cognitive distortions ... the associated depression would lead to improvement in the associated cognitive distortions." is not necessarily so.** It had been shown that in the most depressing environment there may be few suicide, and when cognitive distortion [Despair (underlying SI)] was resolved the underlying suffering (depression) persisted. Also in BPD we can see significant mood lability, depression; the patients can display bright affect at one point of time, but still have significant proneness to cognitive distortion, that can return at any time particularly in response to stress. Our notes under Consid A/2, on RBD also shows why

lifting of the depression (even "rapid lifting" –from the definition of RBD) cannot anticipate the lifting of cognitive distortion or the suicide risk. One specifically could not say that change in one (depression) would predict the change in other when the stakes are as high as people's life.
In summary, as referenced to the more detailed discussion above, the Tollefson reference cannot anticipate our invention, and cannot make our method obvious for those reasons.

It is also notable that Tollefson did not disclose any reference in regard of discussion of alternative rapid onset action antidepressants, or why if at all their methods would be better or worst, than the other methods. We specifically would like to draw attention to this fact (and also that they only included reference in regards to other augmentation strategies to TRD in page 2 (Other publications) in their final patent number US 6,960,577 B2). However, most importantly, Tollefson with the lack of disclosure on risk/benefit and alternative technique did not place the technique to the hand of the skilled in the art.

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

In addition in support of amendments to the claims 106-108 (based on Claim 12 [NMDA receptor antagonist] the following should be noted in the utility:

page 12 of **utility**:

Antidepressants also included are:

Other examples of the NMDA receptor antagonists include, but are not limited to, ketamine,

page 14 **of utility**:
Augmentation strategies used for treatment resistant depression could also be considered for initial treatment.

Use of ketamine, NMDA receptor antagonists as such, and use it as initial treatment, and in combination with antipsychotics therefore had been incorporated in amended claims.

Appendix A, B, and C, of the reply to the first office action, for further explanation and for guidance and enablement:

Appendix A

Appendix A: We should note for reply to "no general theory had been provided" that indeed the opposite is true. Our synthesis of multiple source of information and our conclusion was leading to explanation of how the antipsychotics (antidepressant-antipsychotic combination) may work and target the treatment and the prevention of depression and suicide. It should also be noted that the following conclusions were missed by the artisans of our specialty:

Depression is diagnosed according to DSM based on limited symptoms in addition to depressed mood – as also recited at page 11 of our utility. However, this practice leads our teaching not being recognized.

It is of note that DSM is still useful as the language of the skilled in the art to communicate; but is should not be called as (Diagnostic and Statistical Manual – DSM) but a differential diagnostic manual, as in our view this is what it is useful for. (In other words, by the symptoms what DSM describes, we can differentiate MDD from bipolar disorder for example, but the DSM symptom criterion list is not fully sufficient for diagnosing the depression for severity, or for residual symptoms, as it does not include and recognize many "other" depressive symptoms that we feel should be included.)

In the provisional application (and being also subject of a separate invention [11/034,447]) we were showing that multitudes of other psychiatric symptoms should be included when we test, diagnose and treat depression. {Please see from the provisional application the quotation in the box below)- [*Lettering was added (instead of bulleting) for ease of organizational reference*]. That shows that the antipsychotics would target many "extended" depressive symptoms that are non-DSM, and that are not recognized as part of the depressive symptom list. **B), C); D), E); F); G); H); I); J);** shown below deserve particular attention for our explanation.

So, as we have shown in the provisional (and below) that if the (atypical) antipsychotics target these "other" symptoms that we as psychiatrists do not rely on in diagnosing, testing and treating depression; then the **sum of combining these factors would point out that indeed the antipsychotics are useful in treating depression. That would point out that the antipsychotics (antidepressant-antipsychotic combination) should be used for the purpose of our claims.** With this we support (and show how the antipsychotics are working). [In our provisional we have shown that 1) we should use these antipsychotics for the purpose provided, and 2) should be relying on these "other" depressive symptoms not within the DSM criterion list. The combination of factors mentioned in this paragraph includes that in addition of the direct effect of the antipsychotics on these non-recognised "depressive symptoms", there is an indirect effects of the antipsychotics ("pseudo placebo effect") as well: it has an additional positive psychological effect on the depressed individual, as lifting of one depressive symptom contributes to the lifting of the other by the overall improvement of the patient and by lifting hopelessness. On the other hand the psychological factors are also interacting with morphological neuronal changes – as we have shown in the provisional application and as discussed under "clinical neuroplasticity" in Appendix C;].

Our guidance, no matter how convincing or "obvious" it sounds now – it was not recognized by prior art at the time of our invention. [In fact our guidance in about 4 years later is still not being recognized, despite all of the intense media and FDA attention on this subject].

Quotation for Appendix A: Pasted from provisional (on my copy with font size 14 it was page 35-43 small parts deleted to be concise.) In the provisional lettered headings were bulleted instead. Some sections were made bold here or underlined for added emphasis.) PTO 0316 line 11 on; PTO 0204 -0226:

Page 64: = PTO 0316 line 11 on.

In targeting and specifically designing an approach of trying to solve (most/all) of the patient's problems - ... pharmacologically ... can result in greater success than separate individual strategies alone.

page 35-43 = PTO 0204 -0226:

Let's see some other reasons and other rationales for using the combination of antidepressant antipsychotic medications in clinical depression/major depression (non treatment-resistant major depressive disorder).

A) In a retrospective analysis of suicide committers with major depression showed that many of them have received inadequate treatment. (Forster P., 1994.) ...

Furthermore it had been shown that among the depressed patients who committed suicide many of them actually had psychotic depression that went unrecognized so they were not receiving antipsychotic medications. (Forster P., 1994.) Therefore the adjunctive use of antipsychotic medications could not only enhance the effectiveness of the treatment of depression, but it would also provide a safeguard in case of unrecognized psychotic depression, and therefore – again - prevent suicide. (It had been estimated that a significant proportion, 15% of major depressive episodes fulfill the criteria for psychotic subtype. (Gumnick, J.F. et al. 2000).

In addition, if we were using adjunct antipsychotic medications for the treatment of clinical depression, the overall improvement - as for the group, would also be expected to improve.

Nierenberg had noted that in many cases, the cause of treatment-resistant depression may be an unrecognized psychosis. (Nierenberg. A. A., 1992). (That may explain it again – at least in part – of why did the "treatment-resistant" depression group improve with the addition of an antipsychotic medication.)

B) Cognitive distortions like jumping into conclusions without the analysis of the facts; prematurely getting into conclusions, are characteristic for depression. Cognitive therapy specifically addresses this issue by teaching patients of how to recognize and correct these distortions. Others, (Yapko tape) call cognitive distortions as "global thinking", and report that it is the thinking style of the depressed. It seems however, that there is an overlap between the cognitive distortions; the "mini psychosis" of BPD; and the "full blown psychosis" of psychotics; all of them being out of touch with reality but in

different degrees.

We psychiatrists also know that antipsychotics are not particularly effective in chronic delusions with only one delusional idea (monoideatic delusions), nevertheless we are prescribing them despite of its limited usefulness. (The neuroplasticity model for chronic delusion may explain its relative resistance to medications [Spitzer M. 1999]). Now, that **we postulate** that the atypical antipsychotics may be useful for depression, we may wonder if in fact these medications are - in part - **targeting the cognitive distortions that overlap with psychosis**. In fact it may be worthwhile considering to reclassify depression as a "thought disorder", or at least to note that the overlap between depression (mood disorders), and "thought disorders" is not constricted to psychosis or psychotic depression per se. [For those less familiar with the field of psychiatry, disorders like psychosis, schizophrenia, delusional disorders are listed under the category of "thought disorders, and are treated by antipsychotic medications. Depression – with the exception of psychotic depression – was not (and is still not) considered a "thought disorder. However, the particularly strong cognitive distortions in depressed, through the impaired reality testing, in our opinion do overlap with psychosis. In addition, it had been shown, that antipsychotics do show some antidepressive action,

[added here to examiner see: I) and N) below]

so they may be useful in the treatment of depression. All these points to the direction to view depression – at least in part – as a thought disorder]. With this, the use of antipsychotic-antidepressant combination for the treatment of depression gets further supported.

C) Cognitive distortions also play a role in **anger** attacks that 30-40% of depressed patients display. (Koh, K.B. et al. 2002). A significant association between depression and **violent behavior** in community samples also had been established. (Koh, K.B. et al. 2002). Some reports 28-44% of violent behavior in depressed outpatients. (Hughes, D.H. 1998). Antipsychotics had been used to reduce violence in acute settings, like in ER (Currier, G.W., 2000), and also with psychotic/bipolar patients in long term use. It is also used for 'pathologic aggression' (Collaborative Working Group on Clinical Trial Evaluations 1998 c). Therefore it is questioned again, why don't we use them as adjunct medication in the treatment of depression (major depressive disorder, dysthymia, "double depression"...)?

D) It can be speculated that jumping to conclusions without analyzing the facts may lead to **impulsivity** and may increase the chance for suicide. In fact it is known that impaired reality testing as shown in alcoholism and drug abuse, is associated with significantly increased risk for suicide. Alcohol is associated with 25 to 50% of all suicide and is the second most comorbid factor after depression. (Forster P., 1994.). Therefore addressing **cognitive distortions**, and/or the source of **impulsivity is essential.**

E) Depressed patients (with their strong cognitive distortions) may not only misperceive information coming from the environment (like miscommunications in their relationships leading to social isolation), but also misperceive stimuli coming from their own body

(Szadoczky, E. 2001). In fact increased somatic symptoms are noted in the depressed, (Stahl, S.M. 2002, Kirmayer, L.J. 2001, Kirmayer, L.J., et al. 1993, Szadoczky, E. 2001,), and the majority of the depressed patients present with only physical symptoms to primary care providers (Pincus, H.A. 2001,). This also points out, that part of the problem is with the perceptual disturbance – a symptom, in which just like for delusions it would be logical to use neuroleptics in combination of the antidepressants). [The use of antidepressants in chronic pain and in some somatic problems had been recognized before. (Lynch, M.E., 2001, Bilier, P., et al. 2001, Gruber, A.J., et al. 1996,)].

F) It would be important to reassess the role of cognitive distortions in hopelessness and suicide. A study by Fawcet (as referenced in: cit#16 in Forster P., 1994.), confirmed the predictive value of hopelessness in suicide, and that hopelessness is the greatest predictor of suicide risk beyond the first year. However suicide occurs in only 5% of terminally ill patients and their greatest risk factor is untreated depression (Forster P. 1994.). Therefore **it is not hopelessness per se, but its perception - that is the cognitive distortion** characteristic of depression - **that seems to be the most important factor**. (For strong perceptual disturbances [e.g. hallucinations,] we had been using antipsychotics.). The adjunctive use of antipsychotics with SSRIs and newer antidepressants in the treatment of depression (major depressive disorders and the like) is again supported by this argument.

G) Rumination often seen in the depressed, (e.g. excessive guilt, self-blame, low self-esteem) may overlap with cognitive distortions and also with obsessive-compulsive disorder (OCD). In fact, depression can be viewed that the patients cannot let go of mainly focusing on the negatives. They do ruminate on the negative life events. It is notable, that the adjunct use of antidepressant-antipsychotics was useful in the treatment resistant OCD. (Mohr, N. et al.:2002, Atmaca, M. et al.: 2002). Therefore this medication combination targets another depressive symptom, and substantiates its use for depression, and the decrease of suicide.

[A note to the examiner added: This also overlaps, and can be seen as not letting go of the suicidal ideation, and this type of rumination can be viewed also as related to the automatic thinking of cognitive therapy that deals with cognitive distortions].

H) Social withdrawal (and lack of social support) had been also mentioned as a risk factor for suicide. **Social withdrawal** or lack of social support is found **almost half of suicides** (Forster P., 1994. [cit#26]). We know that atypical neuroleptics (atypical antipsychotics) improve the "negative symptoms" including social withdrawal, at least in psychotic patients. (Purdon, S.E. et al. 2001, Berman, I., et al 1999, Keefe, R.S.E., et al. 1999,). Therefore the use of adjunct atypical antipsychotics or "dopamine system stabilizers" in clinical (non-treatment-resistant) depression would be supported by this logic as well.

I) Additionally, it is known (separate from all other rational that we list here) that antipsychotic medications, atypical neuroleptics have a positive effect on **improving**

depression in psychotic (schizophrenic) patients. They also **reduce hostility** and the risk of suicide in this patient population. (Keck, P.E. J. et al. 2000 (b), Collaborative Working Group on Clinical Trial Evaluations, 1998 b,). In fact in an analysis extending to 1 year, *in psychotic patients* the annual suicide attempt rate with atypical antipsychotics showed a 2.3 fold reduction compared to patients receiving haloperidol, an older antipsychotic. (Glazer, W.M. 1998, also referenced in Keck, P.E. J. et al. 2000 (b),).

J) We also know that **suicidal individuals often find their thoughts constricted** to a narrow range of topics and that they tend to constrain their options prematurely. (Forster P., 1994.) In other words this is **cognitive impairment** and cognitive distortions. Again, the atypical antipsychotic medications had been found to have beneficial effect on cognitive impairment, as measured by psychological testing (at least in psychotic patients). (Purdon, S.E. et al. 2001, Berman, I., et al 1999, Collaborative Working Group on Clinical Trial Evaluations, 1998 a,). That would be an additional support for the adjunctive use of antipsychotic medications with antidepressants in unipolar, non-treatment-resistant depression.

K) Some articles also identify the so-called **suicidal depressive syndrome** (not listed under DSM-IV TR) that patients with major depression at highest risk generally also have feelings of worthlessness, *anxiety*, depressive *delusions* and more *sleep disturbances.* (Forster P., 1994. cit#6). Anxiety itself is a unique and short-term risk factor for suicide, and in patients with major depression, anxiety predicted 93% of suicide within one year of assessment. (Forster P., 1994. cit#5=Fawset).
Patients at highest risk for suicide are those with more severe anxiety combined to depression. (Forster P., 1994. cit#17).
Therefore, again, the addition of a neuroleptic as it has an anxiolytic property would be justified.

The co-occurrence of anxiety and depression is particularly interesting from the standpoint of our analysis.

In their original article treating resistant major depression with olanzapine and fluoxetine the authors (Shelton) did not find a statistically significant improvement in depression with the Hamilton rating scale for depression, but they did find it with the Montgomery-Asberg depression rating scale (Shelton, C. R., et al. 2001 (a).). Nevertheless, the author had find their finding, the improvement of depression, clinically significant. (Written communication from Shelton.)

In our explanation, - what might have gone unrecognized by these authors (and others in the process of replicating the study) – is, that there is a specific, significant difference between these two psychological rating scales. Namely, the Montgomery-Asberg depression rating scale puts a relatively higher emphasis on anxiety (1 in 10), while the Hamilton rating scale for depression has about the ratio of rating *psychic anxiety* 1 in 21. [Somatic symptoms/anxiety are measured separately.]
In addition, the Montgomery-Asberg depression rating scale allows a 0 to 6 measurement

of the inner tension, potentially allowing more emphasis in the statistical analysis. In comparison, the Hamilton depression rating scale there is a 0-2, 0-3, and for anxiety 0-4 scoring. (For replicative studies, it is important of not to use a "simplified" Hamilton rating scale, where there is only a checkmark for the depressive symptoms, not allowing any severity rating: [(See references for the scales: (Stajatovic, M. et al. (eds): 1999.)]. That would make the Hamilton scale even more 'insensitive' to changes in anxiety. Never the less, **what the authors (Shelton) might have actually measured (in coming up with a statistical difference in one scale, but not the other), was the relative improvement in anxiety.** It is known that **antipsychotics reduce anxiety**. [Although this group of medications had been named "major tranquilizers" early on, it was because of their strange quietness or blandness (ataraxia) that the patients ... displayed. (Van Kammen, D.P. 1995).] Undoubtedly, other factors might also play a role in why the combination of antidepressant with atypical antipsychotic medication results in an improvement in the treatment-resistant depression. We have already reviewed above some of the key factors that in our interpretation can contribute to the improvement of depression by adding an atypical neuroleptic, or a "dopamine system stabilizer".

In finding a rational, that why would the addition of a neuroleptic result in an almost immediate positive response in depression; we have to also rely on a psychological explanation. In short, an immediate improvement in any of the patient's symptom would be a direct reinforcement that change is possible, and that would change the patient's expectation. Depressed patients, in general, have a low motivation, a decreased energy and interest, and an expectation that 'why bother', nothing is going to change, nothing is going to help. They have a helplessness and hopelessness. In fact these symptoms are characteristic of depression (and also a significant risk factor for suicide) [for helplessness being an increased risk for suicide see reference: A study by Fawcet (cit#16 in Forster P., 1994.)]. Unfortunately, this is why many depressed people don't seek treatment. It's ironic, that when they come for an evaluation to their doctor, this negative expectation is just being reinforced. They cannot get an immediate relief, the evaluating doctor is asking a lot of questions about painful or negative aspects of their lives, (at times it seems to them that he/she is just dwelling on their problems). At the end of the first visit they are told that the antidepressant cannot help for several weeks. As a result the negative expectation is reinforced, and due to their hopelessness, they may discontinue taking their medication. (see also Yapko tape). In fact nonadherence to the prescribed medication can account for as many as 20% of the cases considered to be treatment-resistant. (Thase, M.: 2002 (b), references >Cit.#11.) About 24% of patients do not inform their physicians that they stopped taking antidepressants. (Demyttenaere, K. et al. 2001). Other publication reports that in primary care, more than one third of patients fail to refill their initial (antidepressant) prescription, and nearly half discontinue it within three months. (Pincus, H.A., et al. 2001,).

Therefore addressing and relieving the **anxiety** - which is present as a **comorbid disorder** in 56.8% of patients with known non-bipolar, major depressive disorder (Zimmerman, 2002) - **would result in a drastic change in the patients' expectation**. Since a positive change had occurred (a relieve in their anxiety, an improvement in their overall feelings), they would show more hope. **Therefore, by pharmacologically**

addressing one symptom, improvement in other – related symptoms, and - in general - in the depression as whole, **can be expected**. That would explain the "immediate" improvement **from the psychological point of view**.

[Added to the examiner to stress the attention: 1) Other alternatives are available by targeting the various symptoms that for the same psychological reason can lead to "rapid onset of action" but with different – better risk/benefit/side effect ratio. The difference was not analyzed by the Tollefson reference, not enabling the clinicians of making decisions to use it right away over other alternatives. 2) Here guidance is also given by us on our explanation of how the antipsychotics can have the proposed effect.]
We will also discuss in Appendix C of how the psychological effects interact with morphological, neuronal changes through "clinical neuroplasticity".

L) Sleep disturbances (insomnia) is one of the depressive symptoms often present. So, addressing this problem early on would result (similarly) in improved compliance and in a more immediate improvement in the overall depressive symptoms as well. (Temporarily adding a sleeping pill - like zolpidem (Ambien), till the depressive symptoms, and with them, the complaint of insomnia would lift - can therefore have a more beneficial effect then what we realize, i.e. the improvement of sleep per se.)

It is important to note, that neuroleptics, in particular atypicals may improve sleep. (Salin-Pascual, R.J. et al. 1999.) That may again point to a benefit of the combination use of these medications with the antidepressants. (See also Eli Lilly patent# WO 99/61027 SSRI-antipsychotic combination use for adverse events associated [with SSRI administration] with the treatment of major depression, partial, or treatment resistant depression.)

M) The more symptoms we address and correct "right away", the better the chances of patient satisfaction and global improvement.
While I was in training, I have heard stories of the "miracle" effect of using stimulants as antidepressant in some medically ill/elderly patients. (Kamholz, B.A., et al. 1996). (See also reference for stimulant use in medically ill/elderly: Satel, S.L. et al 1988; also referenced in: Willner, P. 1997,) I have never put it in this context up till now, but a similar explanation may play a role here that by improving the patients' **energy** we see a quicker response then with other antidepressants. With the global improvement, the patients' expectation changes too, and hopelessness gets less pronounced, or goes away.

(However in defense of biological explanations, we have to note also the following: High placebo response plays a role in the treatment of depression (mean placebo response rate for major depressive disorder is about 30-40% with some studies reporting rates of 70% [Schatzberg A.F, et al 2000,]. Some also suggested with studies supporting that trend, that patients with more severe depression respond well to antidepressants whereas those mildly ill respond equally well to antidepressants and placebo. (Khan, A., et al. 2002, [see also Rush, A.J., 2000, Thase, M.E. 2002 a, 2002 c, and Kirsch, I. 2000, on if the drug and

placebo effects are additive.); However, it is unlikely that placebo response would be the only explanation here. First, here the (adjunct) medication is chosen **specifically to target pharmacologically a specific symptom (the anxiety, cognitive distortions "overlapping" with psychosis; low energy or sleep disturbance respectively), so it is not a "placebo".**

[Added to the examiner we refer to this indirect medication effect in [11/034,447] *as "pseudo-placebo effect"].*

Second, as we can see in the case report with the risperidone-SSRI combination for treatment-resistant depression (O'Connor, M., et al 1998) – at least in one case – it was reported that the patient did relapse despite the resolution of sleep problem (and despite the additional adjunctive use of a benzodiazepine as an anxiolytic); and it did not gave the same result in the improvement of depression as the added atypical antipsychotic did. So psychological explanation on the role of changing expectations is extremely important, but it is not the full answer.)

N) We have mentioned above, that the atypical antipsychotic medications (at least in psychotic patients) show beneficial effect on the **"negative symptoms"** (Purdon, S.E. et al. 2001, Berman, I., et al 1999, Keefe, R.S.E., et al. 1999,). Within the *"negative symptoms"* the following terms are included: *affect blunting* which may correlate to such symptoms in depression as decreased interest, concentration, and psychomotor retardation. The term *anergia* correlates with the symptom of decreased energy. *Alogia* if due to depression may be because of decreased interest, psychomotor retardation, or decreased energy. *Social withdrawal* may occur for many reasons, but decreased interest, concentration, psychomotor retardation, guilt, and hopelessness (which are all symptoms of depression) can also play a role. The above is another reason of why the atypical neuroleptics could provide a benefit in the treatment of depression – as adjunct to the antidepressants.

It is extremely important to emphasize, that our synthesis of data, and the conclusions that we have drawn were missed by the skilled in the art.

Appendix B

Appendix B: Here we are revisiting enablement for preventing depression or the progression, or relapse. (This is an additional response to the examiner as he raised these issues as above Reply 12, and [Reply-14, 16, 17, 19, 20,]):

First, it should be noted as we have discussed under the line-by-line reply (e.g. Reply-14) that prevention does not need to be 100%, [the term preventive medicine is also not 100%].

Second it should also be understood by the skilled in the art (and as a term used at the time of our invention) that prevention in depression is meant an intervention for those who are depressed or had been depressed before at least at one point in their life. That is

medications are not given prophylacticly for healthy people for those never being depressed before.
Third, it is also understood by the skilled in the art, that if claiming a preventive effect for a combination of medications the two compounds given together has to be better than any of the single compound in that combination, otherwise the risk/benefit/side effect analysis would not permit the combination use.
Having cleared all these we should further discuss of what else was already known by the skilled in the art at the time of our invention:

We have mentioned *in our provisional at page 59 (last paragraph)= PTO 0286:*
"The issue of how long one should take an antidepressant needs to be discussed with the patient. There are only general guidelines for this. The "rule of thumb" varies by how many times the patient relapsed (possibly also taking into account the family history), the patient's age, and (with the newer safe antidepressants) if the patient wants to risk a relapse. These guidelines are known to the clinicians."
Therefore, it was known that the continuation of antidepressant (but not antipsychotics) may be preventive against the recurrence of depression. [See also (1) below].

At the time of our application the following was also known:

- (1) compared to patients whose **antidepressants** were discontinued, those with **continued** treatment showed much **slower relapse risk** (and more serious illness/more previous episodes or a chronic course was strongly associated with higher relapse risk after discontinuation of antidepressant but no effect on response to continued treatment. (Viguera, A.C. et al Discontinuing Antidepressant Treatment in Major Depression, Harvard Rev Psychiatry 1998; 5:293-306.)
- (2a) **Cognitive therapy** (either alone or in combination with medication) evidenced less than half the relapse rates (Evans M.D. et al Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry 1992; 49:802-808), and **lowered the relapse and recurrence rates**. (Shaw, B.F. Cognitive-behavior therapies for major depression: Current status with an emphasis on prophylaxis. Psychiatr J. Univ Ottawa, 1989, 14(2):403-8). – but as shown in the following article was still insufficient for most patients to achieve full recovery:
- (2b)16 weeks of specific forms of treatment, cognitive behavior therapy (interpersonal therapy, imipramine [antidepressant] and clinical management, or placebo and clinical management) was insufficient for most patients to achieve full recovery and lasting remission. (Shea M.T. et al Course of depressive symptoms over follow up. Findings from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. Arch gen Psychiatry 1992; 49:782-787).
- **(3) Fully recovered patients were at lower risk of relapse** (Thase M.E. et al Relapse after cognitive behavior therapy of depression: Potential implications for longer courses of treatment. Am J Psychiatry 1992; 149:1046-1052). – Patients with **relative high level of depressive symptoms relapsed more often** than those who had little or no residual symptoms. (Cognitive therapy and

pharmacotherapy for depression. Sustained improvement over one year. Simons A.D. et al, Arch Gen Psychiatry 1986; 43: 43-48).

- (4) As in the 1994 Fava reference:
  The possibility that antidepressants may sensitize neural tissues and resulting in a dependence, and "prolonging the syndrome" was also mentioned. The possibility of antidepressant (when used for other than depression) unmasking the depressive diathesis (causing depression) was also mentioned. Loss of antidepressant effects during continuation therapy had been attributed to tolerance as it responded to increased dosage. Not just stressors in association with the first episode of depression, but antidepressant drugs possibly also triggering such a sensitization and gene expression was also postulated. It was also said that long term use of antidepressant drugs may increase the biochemical vulnerability to depression and decrease the likelihood of subsequent response to pharmacological treatment. It is also raised if antianxiety drugs may be depressogenic. (Fava G.A. Do antidepressant and antianxiety drugs increase chronicity in affective disorders? Psychother Psychosom 1994; 61:125-131). [We also had references in our utility similar to this, see *I)*; under Reply-12]. [Regarding (2) above, we have made reference to that fact in our provisional application. Please see paragraph 12 in Appendix C below].

Now with all this known to the skilled in the art; our teaching in the provisional application discussed above in Appendix A is showing further evidence and an enablement that indeed the combination of antidepressant-antipsychotic medication would be useful for the prevention of depression and depressive relapse: That is that in Appendix A we showed that there are many other depressive symptoms that the DSM ignores, and does not includes in its list of criteria for depression; yet these symptoms should be recognized as part of depressive symptom list. Targeting the relieve of these symptoms (with antipsychotics or antidepressant-antipsychotic combination) would result in the overall improvement of the patient. Relieving these "unrecognized, non-DSM" symptoms would lead to a better or full recovery. Reference under (3) above recites what was already known at the time of our invention, that is "**fully recovered patients were at lower risk of relapse.**" Therefore, our synthesis, and our teaching on the unrecognized non-DSM symptoms, and that the antipyschotics are effective in relieving these symptoms provides further enablement, and shifts the prevention of depression from unpredictable to predictable. A better treatment (through the antipsychotic-antidepressant combination), also targeting the "extended" depressive symptom list would give a better chance for full recovery and for a lower risk of relapse.

A strong emphasis should be placed on that these conclusions and inventions were missed by the skilled in the art as it was also admitted by the examiner (above box of Reply-14).

The references we gave above, and under Reply-12 and Reply-19 shows that the depression prevention is a crowded art.
As the reference above under (2b) shows, even with antidepressant medication and cognitive therapy there is still a need for improvement and there is still an unsolved long

felt need, for which our invention can be useful. We have also shown something that escaped others attention – that the symptoms of depression are more extensive than the criterion list in DSM IV-TR. We have also shown how the antipsychotics effect on these symptoms can make the depression treatment more effective through psychological, neuronal changes [and even through gene expression]. (See Appendix C)

Appendix C

Appendix C: We will discuss here the interaction between the psychological, medication and neuronal changes [and even between genetic expressions]. (We also need referring back to the above Appendix A, where we already discussed interaction between psychological effects and medication effects.) **No claims in this application had been drawn regarding Appendix C**, but it relates to a question that the examiner was lacking as a guidance (above Reply-20). Since we had even detailed in our provisional such an innovative synthesis between the psychological, medication effects and the neuronal changes, therefore we revisited this issue here to attend to what the examiner was missing in the 1st office action.

In the provisional application (being also subject of a separate invention [11/034,447]) we have discussed research on neuroplasticity (the adaptation of the brain to change) in other areas than depression, followed by our synthesis of how that knowledge can be used in education on treatment of depression.

*In the stroke victims the **strong (not paralyzed) hand** needs to be **"immobilized"** with placing a large mitts on it, so that the patient cannot use it and be **forced to use the week hand** (the paralyzed hand) with which he or she is instructed to **turn dominos over and practice that** for six hours a day. **Change in corresponding neuronal connections** results in regaining the lost function.*

Therefore, we came up with the "domino" metaphor as an analogy taken from the rehabilitation of the stroke victims and that metaphor to be used in the rehabilitation of the depressed.

*The **strong negativistic (pessimistic) thinking**, with the global thinking, jumping to conclusions, cognitive distortions needs to be **"immobilized"** so that the depressed person's **"weak positive thinking pattern"** and the corresponding neuronal connections (through neuroplasticity) could be mobilized, and **strengthened with practice,** so that the normal, non-depressed function would be regained. This strengthening can be achieved through many ways, 1) through teaching cognitive therapy (catching and modifying [negative] automatic thinking, using cognitive analysis; 2) changing the situation and with this changing the predominant thought content; 3) using therapy to change the meaning attributed; and 4) using medications (or other means) that "helps either immobilizing the negative thinking and cognitive distortions, or doing so by*

relieving the symptoms of depression" or "strengthening or facilitating the neuronal growth in the neuroplasticity model to facilitate the recovery".

The opposite is true for this neuroplasticit change if we are forced to practice a negative thinking pattern. That would result in depression. The "Stanford prison experiment" if analyzed retrospectively, it proves that harmful effect. We gave examples to this in the provisional as well:

Quotation for Appendix C: Pasted from provisional Some sections were made bold here or underlined for added emphasis.) On "clinical neuroplasticity", and interaction of psychological, (medication) and neuronal changes in depression.
Pasted from provisional pages 50-57 (if with font size 14) (parts deleted) = PTO 0251-0277:

Although some may use the terms synaptic plasticity or neuroplasticity as synonymous, it may be better to separate the two phenomena. Synaptic plasticity as it relates to depression (and learning), is primarily referring to changes in the cellular, synaptic and molecular levels, with the focus on glutamate neurotransmission and NMDA receptors. One of the primary interests is on the volume loss of the hippocampus, with possible neuron loss during depression. It had been questioned if stress and elevated glucocorticoid levels (through oxygen radicals and "programmed cell death") may cause hippocampal neuron loss associated with subtypes of chronic depression. (Lee, A.L. et al, 2002; Duman, R.S. et al. 1999,). There is evidence that stress will cause a regression of dendritic process in hippocampal neurons producing loss of neuronal volume, this however, has been shown to be reversible with the cessation of stress. (Lee, A.L. et al, 2002,).

The synaptic plasticity model of depression also overlaps with the theory on the failure of neurogenesis (lack of brain cell growth) linked to depression. (Vogel, G. 2000). Neuroimaging techniques show smaller hippocampi in depressed patients, and antidepressant drugs and electroconvulsive therapy (in animals) show significantly more newly divided cells in the hippocampus. This is an addition to the recent discovery that had shown that the brain keeps producing new neurons into adulthood. (Vogel, G. 2000, Duman, R.S., et al 2000,).

Looking beyond the changes in the hippocampus and receptor level in depressed patients, it would be worthwhile to separate the term synaptic plasticity from neuronal plasticity.

Neuronal plasticity, the capacity of the brain to respond to changes (Spitzer, M. 1999,) had been extensively studied in some other conditions where the cortical representations of somatic perceptions can be mapped. (As the brain has no sense of pain, neurosurgeons could operate on patients while they were conscious [in local anesthesia or "woken up" after their sculls were opened] for example to remove a tumor, but to preserve brain areas that are essential to speech, vision or movement. During such operations it was discovered that part of the cortex that is responsible for processing touch sensations and is representing the different areas of the body, has a map-like structure, called "homunculus" in the cortext. Not only touching, but all senses are represented in

topographical cortical maps. [See also: Spitzer, M. 1999,]).
What ~~is~~ the most intriguing is, that these cortical maps or cortical representations are not fixed, but have the ability to change if the input is changing (i.e. to show neuroplasticity). In a congenital malformation called syndactyly, the fingers are attached to each other (like in a fetal webbing). After the fingers are surgically separated, the borders between their cortical representations emerge in one week. (Mogliner et al. as referenced in Spitzer, M. 1999,). The opposite was also shown in animal experiments sawing the fingers together. Changes in cortical representation do follow this procedure.
In a different experiment (seen at PBS), a human volunteer was blindfolded for about two weeks, and it was found through a non- or minimally invasive procedure, that other brain areas started to "took over" the now unused visual cortex, and the cortical representations of the fingertips (touching) had increased.
It is interesting to compare that while it takes weeks for the antidepressants to start working, it also took week(s) to see neuroplasticity changes in the above experiments. For a more complex adaptation neuronal changes may take even a year (e.g. cochlea implant). (Spitzer, M. 1999,).

The above experiments are looking beyond the changes in the hippocampus (and are not constricted to the receptor level). Different emotions, or the changes in depressive disorders are not limited to the hippocampus, and other brain areas are also involved.

Beyond the cellular changes in the hippocampus, and beyond the explanation of changes at intracellular level, the only strong support for the neuronal plasticity of depression, that we have seen was the argument that the therapeutic action of antidepressants requires weeks, even though these medications block the reuptake or metabolism of norepinephrine (NE) and serotonin (5-HT) much more rapidly. The conclusion was that therefore the treatment of depression involves adaptation or plasticity of neural systems. (Duman, R.S. et al, 1999,).

Yet **it would be interesting to see a synthesis of clinical findings, supporting the neuronal plasticity model of depression from the clinical standpoint**. Below we will present our viewpoint that brings the psychological and biological explanations together, and provides further understanding of depression. [These were never presented in this context before].

First we'd like to start with the "domino metaphor" (or "practice makes a master" metaphor).
Although traditionally it was believed, that if stroke victims did not regain the function of their arm within a few months, then it was little hope for recovery, we know it now that this is no longer true. Supported by clinical data and not just animal experiments, we know that persons with stroke "learn" of not to try using their paralyzed arms or legs, and as times goes on this becomes an increasingly powerful conditioned response. However, by placing a restraint (a large stuffed mitt) on the patient's functioning arm, he/she is forced to overcome the tendency of not using his/her weaker arm. With physical therapy they are coached 6 hours a day to practice and improve the movements of their weak

extremity. They are given tasks like turning dominos over (and cheered for their success). With practice and repetition comes a dramatic change within a few weeks. This phenomenon had been explained as a result of "an increased recruitment of neurons surrounding the area of the primary damage caused by a stroke". The neurons that haven't been killed by the stroke, but are in the vicinity of the damage are sending out connections with other neurons. (Restak, R.M., 2001 and corresponding PBS video). This is the neuronal plasticity that we have also seen in other examples above. In principles we see a similar phenomenon when children's good eye is covered to force the weaker eye to "learn to see". With practice we are relying on neuronal plasticity in a therapeutic way.

Now, if this true on other areas, why wouldn't it be true for depression, or for the treatment of depression? In fact we have unpublicized data available to support that most likely the same is true for depression. Depressed people tend to focus on the negatives, and tend to ignore seeing the positives. Cognitive therapy teaches us to do similar repetitions, that is, to catch ourselves to have (negative) automatic thoughts, and make necessary corrections by doing an analysis of the facts on both the negative and the positive side. This is the practice that is similar to the "repetitions of the movements" seen in stroke victims above. We just do not have a god visible "mitt" that would force us doing this practice. However medications do help exactly in that direction: We have mentioned above, that the problem in depression is rumination, the repetition and overt focus on the negatives, with cognitive distortion. Actually SSRIs used for treating depression are also working to reduce OCD symptoms, "the rumination". We suggested above that neuroleptics may also be helpful in many ways, and are expected to help decreasing cognitive distortions, that are so characteristic of and contribute to the depression.

However, let see some experiments from decades ago can be applied in this context, so that with our current knowledge they would clinically support the neuroplasticity model of depression.
One of the experiments, (Haney, C., et al. 1973, also referenced in Yardley, K.M. (1982 b), ... Yardley, K.M. (1982 a),), although was not designed to do anything with depression, but has a great relevance to it, as it shows the importance of how detrimental can a 'negative practice' be even in "as-if" (or role play) situations. In a Stanford experiment they recruited normal healthy volunteers who agreed to take part of a "prison simulation experiment" for up to two weeks. They randomly assigned them to be either "prisoners" or "guards". Unlike the guards, who had some minimal warm-up to the as-if event, 'the prisoners were covertly inducted, without their conscious cooperation. For the sake of "realism", they were arrested in the early morning, on false burglary charges, by actual members of the city police who were cooperating with the experimenters. The prisoners were then subjected to police interrogation and taken blindfolded to the simulated prison.' (Haney, C., et al. 1973, also referenced in Yardley, K.M. (1982 b),). The "prisoners" were further subjected to humiliating and frustrating experiences (and their queries to the police if this had to do anything with the experiment were ignored). After a week the experiment needed to be prematurely terminated, "due to the ensuing emotional disturbances amongst the participants, particularly amongst the prisoners". (Yardley, K.M. (1982 b),). The "prisoners" were feeling powerless, loss of control to the

point of oppression, frustration, 'emasculation', anonymity, and arbitrary rule. The later in this case is really resulted in "learned helplessness" that we know as an important causative factor in the development of depression. While this experiment from the early 1970's looks cruel, and we can all hope that this kind of "experiments" can no longer be done today, they show something, that artificially practicing and focusing on the negatives, or be forced to focus on the negatives even in an "as-if" experiment would result in an unwanted emotional disturbance. This is exactly the opposite of what we therapists and health care professionals want to achieve, and an example that "neuroplasticity" works both ways. In a commentary on the above 'experiment' Yardley notes that the outcome would have been different if the participants would have been brought out of the as-if situation every few hours or so to remind them of the as-if framing. (Yardley, K.M. (1982 b),). That means of shifting the balance between the negatives and positives. This is what depression therapy is all about when we give the patients the tools of doing this.
In another experiment unemployed actors were recruited for a depression study. They were paid volunteers, and were asked to act and think as-if depressed, to walk slowly with a bended posture, and think that they are no good, etc. In two weeks they have shown biochemical and other signs of depression, and the actors reported that they had difficulty snapping out of the depression after the experiment was over.
All of the above supports not only the "clinical neuroplasticity model of depression", but also the importance of practice to overcome depression. In this context this is very similar to the therapy of the stroke victims mentioned above. This "domino metaphor" (or "practice makes a master" metaphor) can also be used clinically to motivate and educate patients about depression, and depression treatment.

The above – the neuronal plasticity model - can also give an insight to the course of depression, and to the 'natural' tendency to relapse, of why is that so easy to relapse, if one stops the medication(s), or stops the 'positive "domino" practice'. It was shown, that practicing cognitive therapy can be protective of the depressive relapse, and this is supportive of this view. It was also shown that the combination of antidepressant and cognitive therapy is superior to either treatment alone. [see Thase].

One of the reasons for why the neuroplasticity model of depression is still lagging behind the other observations on the brain's power to adapt is that our technology did not allow us to "map" the cortical representations and changes that occur with the depression. Our brain imaging techniques are improving (George, M.S. 1994, Ketter, T.A., et al. 1994, George, M.S., et al. 1994, Rubin, E., et al. 1994,), but there is another way to assess and "map" changes in the brain.
The cortical representation of one's "inner world" may be also reflected by one's vocabulary. It had been shown, that in children, at an early age, words referring to the imaginary world (like fairies, dragons, etc.) shows a relative high ratio to reality based words in comparison to adulthood. (Deme, L. personal communication, Deme, L. 1975,). This "mapping" of children's vocabulary is in turn ... also correlates with the finding that children has a greater involvement in fantasy, and have a higher hypnotic susceptibility. (Migaly, P. 1991).

Although it is not the same, but assessing patients depression (or feelings) with a psychological test, that we propose for a more accurate assessment of depression, can serve as a "mapping" tool. ...With an analogy it is like the vocabulary in the RAM or the hardware of speech recognition software. The words used (thought/ruminated) more often are stored upfront (RAM), but other words are still recognized that are stored in the hardware. So mapping of the neuroplasticity changes occurring during or in the recovery of depression is also possible with a psychological tool relying on the vocabulary. (One has to be careful though to balance the testing with counseling and of not to alter with too frequent testing the "positive – domino – practice" encountered in therapy, or by the positive effect of the medications).

In helping someone to come out of depression (and one's inner world of focusing on the negatives), it had been shown that physical exercise has a value, and an antidepressant effect. (Russo-Neustadt, A., et al 1999, Blumenthal, J.A., et al 1999,). We also know, that in chronic pain, that frequently also overlaps with depression, physical activity has a beneficial effect. Moreover, physical exercise was also shown to be of value in connection with learning and neuronal plasticity. These similarities are intriguing.

It had been questioned before that if for the depressed patients everything would go exactly their way for a few solid weeks, without disappointments, rejections or criticism while everybody would love them, would their depression go away? (O'Connor, R. 2001 p23). Well, it depends. These circumstances could definitely make everybody's life easier, but recovery to a large extent depends on "the domino metaphor" practice above. (However, the "optimal circumstances" raised in the above question are so important that in our upcoming book we are paying attention to on how to achieve the most and get a harmony, a 'full life' not just recovery from depression.)
In fact the closing remarks in a book where there is a lot of discussion about neuronal plasticity emphasises that we all should "watch our mental diet". (Spitzer, M. 1999,). In this the author means that we should watch the input we receive (e.g. through violent movies, discouraging news from within the society).

In summary for this section in looking the global picture, that is the role of neuronal plasticity in depression, the psychological and biological explanations indeed do blend together.

Additional references for Appendix C (from the provisional) are as follows:

Blumenthal, J. A., et al. Effects of exercise training on older patients with major depression. Arch Intern Med. 1999, 159:2349-2356.

Deme, L. (Some aspects of children's linguistic education.) [in Hungarian] Tiszatáj (Szeged), 29, 1975, 16-21.

Deme, L. Personal communication. Káptalanfüred, Hungary.

Duman. R.S. et al. Neural plasticity to stress and antidepressant treatment. Biol.

Psychiatry 1999, 46: 1181-1191.

Duman, R.S., et al. Role of gene expression in stress and drug-induced neural plasticity. TEN (The Economics of Neuroscience), 2000;2(4), 53-70.

George, M.S. Introduction: the emerging neuroanatomy of depression. Psychiatric Annals, 24:12, 1994, 635-636.

George, M.S., et al. Activation studies in mood disorders. Psychiatric Annals, 24:12, 1994, 648-652.

Haney, C., et al "Interpersonal dynamics in a simulated prison". International Journal of Criminology and Penology, 1973, 1; 69-97.

Lee, A.L., et al. Stress and depression: possible links to neuron death in the hippocampus. Bipolar Disorders 2002, 4: 117-128.

O'Connor, R. Active treatment of depression. WW Norton & Company, New York, 2001.

Restak, R., The secret life of the brain. Dana Press and Joseph Henry Press 2001.

Rubin, E. et al. Brain imaging studies of antidepressant treatments. Psychiatric Annals, 24:12, 1994, 653-658.

Russo-Neustadt, A., et al. Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. Neuropsychopharmacology, 1999, 21:5, 679-682.

Spitzer, M. The mind within the net. Models of learning, thinking, and acting. A Bradford Book, Cambridge, 1999.

Thase, M. (2002 a): Comparing the methods used to compare antidepressants. Psychopharmacology Bulletin: Spring 2002-Vol. 36, Suppl.1 4-17

Thase, M. (2002 b): What role do atypical antipsychotic drugs have in treatment-resistant depression? J. Cin. Psychiatry 63:2, February 2002, 95-103.

Thase, M. (2002 c): Studiing new antidepressants: if there were a light at the end of the tunnel, could we see it? J. Cin. Psychiatry 63 (suppl2) 2002, 24-28.

Thase, M. Treatment issues related to sleep and depression. J. Cin. Psychiatry 61; (suppl 11)2000, 46-50.

Vogel, G. New brain cells prompt New theory of depression. Science. 290, 2000, 258-259.

Yardley, K.M. (1982 a) On distinguishing role plays from conventional methodologies. J. Theory Soc. Behaviour. 12; 1982, 125-139.

Yardley, K.M. (1982 b) On engaging actors in as-if experiments. Journal for the Theory of Social Behaviour. 12(3) 1982, 291-304.

In response to the examiner's note the above shows that we have even addressed the connection between the psychological and neuronal factors. It is notable that this synthesis, and our conclusions were missed by the skilled in the art.

Secondary Factors

The following secondary factors support unobviousness of our patent. (We will discuss the secondary factors in more details after this list):

1) Previous failure of others (See e.g. FDA directors' inability to give adequate solution)
2) Solves insoluble problem (See e.g. FDA directors' inability to give adequate solution)
3) The invention is in a crowded art (There are a lot of inventions on antidepressants)
4) Unsuggested modification (e.g. for initial treatment substantially in everybody depressed; treatment of 1st choice; looking the interest of a group; lower dose of antipsychotics; etc)
5) Unappreciated advantage (for the paradoxical effect of antidepressant worsening depression; for the development of tolerance against the antidepressants; for antidepressants causing suicide; prevention, modifying course of illness, SI prevention, etc)
6) Solution of long felt need (not solved by others) (e.g. SI prevention); (See FDA director's inability to give adequate solution; see Tollefson / Eli Lilly and Chappell / Pfizer not recognizing the use for preventing the paradoxical effect of antidepressants worsening depression or causing suicide; and not speaking up in the midst of FDA and media attention.)
7) Contrary to prior art teaching (even in the light of intense media attention, and highly recognized experts like FDA chiefs)
8) Synergism (described in the application)
9) Prior art references would not operate in combination (lower dose of antipsychotic is better; initial treatment for the interest of a group is essential;)
10) References teach away from combining (or its use), (This, in the light of intense media attention makes this factor much stronger! In addition, lack of teaching the same as in our invention (with the details), should be also considered a teaching away in our case, when it would be the legal duty of drug companies to reveal and teach that knowledge – if realized by them – and them not doing so would expose experts like the drug companies and the FDA to significant legal liabilities. The lack of teaching by these experts (FDA and drug companies) the same as in our invention (with the details), would be the violation of the law if indeed they would have come to the same conclusions, or they would anticipate from their prior art the same conclusions that we have made). – In this regard the examiner's quotation is also applicable: "Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but **compensation for its successful conclusion.**" And "patent protection is granted in return **for an enabling disclosure of an invention**..."
So, teaching away and lack of teaching the same by others (in intense media and FDA attention), as secondary factors are all supporting the patentability of our invention.

11) Most recently the FDA asked AstraZeneca pharmaceutical company (in approving quetiapine for bipolar depression), that a black box label (about suicidality) be included, for quetiapine an atypical antipsychotic similar to that became a requirement for all SSRI and other antidepressants; therefore teaching against our invention that the antipsychotics would have a protective effect. (The drug company complied, and I was notified about this by mail in November of 2006. – A copy of this letter and the new labeling information is enclosed for your reference).

Secondary factors
And
Our **specifics of inventive points:**
1; Prevention of suicide with the use of the medication or combination, (low dose antipsychotics), and through initial treatment taking the interest of the group and the individuals
2; Prevention or treatment of the paradoxical effect of antidepressants
3; Prevention of the progression of the disease, modifying the course of the disease.
4; Prevention of relapse.
5; Cognitive distortion
6; Smoking cessation (in non-psychotics) with or without other treatment modalities

	1	2	3	4	5	6
Previous failure of others	yes	yes	yes	yes	yes	yes
Solves insoluble problem	yes	yes	yes	yes	yes	yes
The invention is in a crowded art	yes	yes	yes	yes	yes	yes
Unsuggested modification (e.g. for antidepressants causing suicide; for initial treatment (for most) everybody – as described; lower dose of antipsychotics; etc)	yes	yes	yes	yes	yes	yes
Unappreciated advantage (prevention, modifying course of illness [being superior than antidepressants alone] etc)	yes	yes	yes	yes	yes	yes
Solution of long felt need (not solved by others) (e.g. SI prevention)	yes	yes	yes	yes	yes	yes
Contrary to prior art teaching (even in the light of intense media attention, and highly recognized experts like FDA chief)	yes	yes	yes	yes	yes	yes
Synergism (described in the application)	yes	yes	yes	yes	yes	yes
Prior art references would not operate in combination (lower dose of antipsychotic is better)	yes	yes	yes	yes	yes	yes
References teach away from combining (or its use), (Again this is in the light of intense media attention. Lack of teaching (in addition of teaching away) should be also considered a teaching away in this case when not doing so would expose large entities to significant legal liabilities or would be the violation of the law).	yes	yes	yes	yes	yes	yes

Secondary factors continued, (discussion and details):

News that appeared after our PTO application about the FDA warning on risk of antidepressants causing suicide had been heavily and repeatedly publicized in virtually all US newspapers and all media.
In the intense FDA, professional and media attention, even up to date, the "obvious conclusions" stated by the examiner was not followed by the skilled in the art, and many years later, there is still teaching away from our invention. One cannot expect that a good number of leading projects some also sponsored by the

NIMH, or from national to international forums, would all teach away (and keep doing it from 2002-2005), if these "conclusions" would be really obvious from prior art as the examiner have repeatedly stated that. In addition all these teaching away were published in leading professional journals. The editors of these journals did not only accepted these teachings against our invention (years later), but did so without even making an editorial comment. With the need of solution (our invention) and that need being in the FDA, professional and media attention one cannot say that others would come to the same conclusion at the time of our invention, as we did, as one cannot expect that many leading professionals and the FDA, and the NIMH who were sponsoring studies that teach away would be all blind to these facts.
One cannot expect that the directors of the FDA would embarrass themselves in their national front page interview of being perplexed about a lack of solution (on antidepressants causing suicide) and being perplexed of not knowing what to do if they would have recognized our teaching or if the same conclusions would have been "obvious" and could have been drawn from prior art. (Please see the FDA newspaper interview from March 2004 and December 2006 in the enclosure).

Therefore secondary factors strongly oppose the obviousness rejection.

(Please also see these teaching away and references/ publications from 2002-2005 under **Consid: 2) here:**

Consid:2): Teaching away (publications from 2002-2005):
(A,) Texas Algorithm Project, (B,) The Berlin Algorithm Project – and **(C,) The Algorithm Study of the German Research Network on Depression** – and **(D,) the Sequenced Treatment Alternatives to Relive Depression (Star*D)** and NIMH-funded multisite trial – are <u>all teaching away</u>:

Consid: 2)-A: Texas Algorithm is teaching away (see figure 1 of publication in the enclosure.)

Now, we have discussed how important it is to use the risk/benefit (side effect) analysis, in light of alternatives of other strategies for faster (rapid) onset antidepressant action. We have also discussed, and will further elaborate on it below how the FDA and others were teaching away from our method (or not even recognizing our method).

Texas Algorithm is a nationally recognized initiative for giving guidance to different mental illnesses, and as such many US states (about half of them) have adapted the Texas Algorithm. [See e.g. publication by Dewan, N.A. Psychiatric services 2003 Vol 54/12 1646-49 on implementing this in Ohio]. These states made the Texas Algorithm mandatory and to be used in the state psychiatric facilities (including State hospitals). Pennsylvania adapted this under the name of PennMaps. I have received from a pharmacy reminders to use the Texas Algorithm adaptation under PennMaps on community (non-state facility) patient as well. (The adaptation of the Texas Algorithm was done in different stages, starting with the treatment of schizophrenia with plans to follow this mandated protocol for other mental illnesses). We are not focusing here on whether this policy by the states is correct or not, we are simply pointing out of how widely accepted the teaching of the Texas Algorithm is. So, the Texas Algorithm (as referenced below for the treatment of depression [MDD]), is teaching away from our invention not only in regards of "other" fast action antidepressant alternatives, but also as to not to use combination at the beginning of therapy. It teaches away by starting the treatment of depression as monotherapy, and therefore teaching of not to use treatment resistant depression (TRD) methods as initial treatment at all. Actually, it did not even occur to them, that a more vigorous

treatment as initial treatment would be useful, for the prevention of suicide. So this is another factor to show, that our methods are not obvious to the skilled in the art (contrary to the examiner's statement).

Their teaching away from our invention, supports the patentability of our claims.

Reference: Tiverdi M.H. et al Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project Arch Gen Psych 2004 Vol 61 669-680.

Consid: 2)-B) and Consid: 2)-C): and Consid: 2)-D): (B,) The Berlin Algorithm Project – and (C,) The Algorithm Study of the German Research Network on Depression – and (D,) the Sequenced Treatment Alternatives to Relive Depression (Star*D) and NIMH-funded multisite trial – are all teaching away:

References:
Aldi, M. et al Algorithms for optimizing the treatment of depression: Making the right decisions at the right time. Pharmacopsychiatry 2003; 36 Suppl 3: S222-S229.

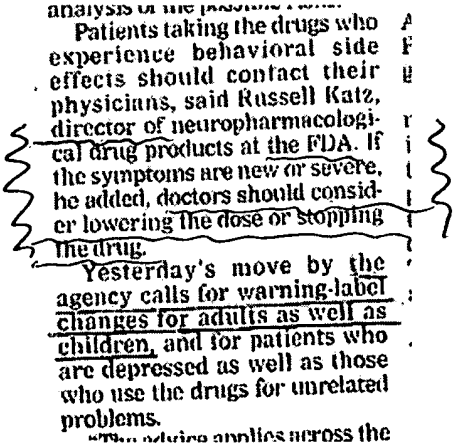
Standardized Stepwise Drug Treatment Regimen (SSTR) – teaching away:

Aldi, M. et al Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: Result of a 2-year observational algorithm study. J Clin Psychiatry 2002, 63:9 782-790.

In addition; Effectiveness study is also teaching away:

Remission rates with 3 consecutive antidepressant trials: Effectiveness for depressed outpatients. J Clin Psychiatry 2005; 66:670-676.

In addition, when the FDA director was interviewed on the new FDA warning on the antidepressants causing suicide, he was teaching away from our invention, suggesting decreasing or stopping the antidepressant (leaving patients having suicidal thought and their doctors with very limited options). This has happened after our patent application. So secondary factors intensely support that prior art did not anticipate our invention, and they were teaching away from it:



analysis of the possible risks.

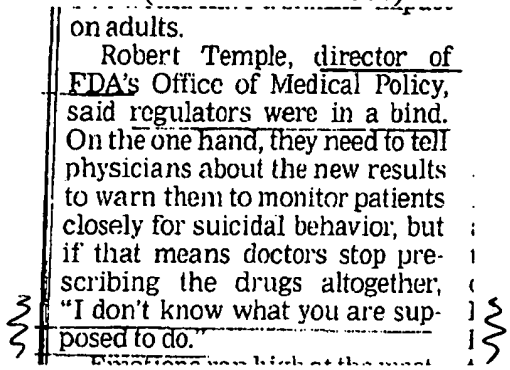
Patients taking the drugs who experience behavioral side effects should contact their physicians, said Russell Katz, director of neuropharmacological drug products at the FDA. If the symptoms are new or severe, he added, doctors should consider lowering the dose or stopping the drug.

Yesterday's move by the agency calls for warning-label changes for adults as well as children, and for patients who are depressed as well as those who use the drugs for unrelated problems.

The advice applies across the

(Please see the FDA directors' statement below and the full article in the enclosure.)

In addition most recreantly this teaching away repeated itself as demonstrated by another front page interview with a different FDA director (December 14 2006).



on adults.

Robert Temple, director of FDA's Office of Medical Policy, said regulators were in a bind. On the one hand, they need to tell physicians about the new results to warn them to monitor patients closely for suicidal behavior, but if that means doctors stop prescribing the drugs altogether, "I don't know what you are supposed to do."

The FDA is perplexed about the lack of solution (and seemingly unaware of our solution or application and PTO publication). (The FDA never contacted us asking for any further information). The FDA director stated that he does not know what he is supposed to do [or suggest].
(Please see the FDA director's statement below and the full article in the enclosure.)

We on the other hand have made an extensive risk/benefit analysis, and have provided enabling guidance. (No matter how convincing or "obvious" it sounds now – our teaching was not recognized by prior art). [In fact our guidance is still not being recognized about 4 ½ years later, despite all of the intense media and FDA attention on this subject].

Furthermore, major pharmaceutical companies could be hold legally liable of not being forthcoming to the regulatory agency and the public with a solution if indeed they would have concluded the same as we did in our application. (The same liability may apply for the FDA). (Some of these major pharmaceutical companies were even cited by the examiner in the Tollefson, and Chappell references). **So before anyone would say that our invention is obvious, or even that our reasoning and reply to the 1st office action is obvious from the prior art, one should consider the vast amount of secondary factors we have listed here.** The final proof is not that our invention should have been anticipated, but whether it was at the time of the invention. As the secondary factors show, this was not the case, and therefore these secondary factors support the novelty and unobviousness of our invention.

Additionally , Tollefson had been actively involved (with his studies working for Eli Lilly), when Eli Lilly drug company was sued that fluoxetine (Prozac) was allegedly causing suicide in some patients. That was well over 10 years ago. [I have no doubt that antidepressants save life (as for the group), but in some cases they may cause SI as the recent FDA warning draw attention to that effect. (This FDA warning happened after our patent application)]. So Tollefson and Eli Lilly in filing their patent would have had an increased duty to specifically give guidance and draw attention to any innovation on prevention of suicide or on the paradoxical effect of antidepressants (in addition that adequate guidance is a requirement anyway). They failed to do so. Tollefson and Eli Lilly would have had an increased duty to specifically give guidance and draw attention to our claims on the solution to preventing suicide and on solving the paradoxical effect of the antidepressants worsening depression, would they have felt that their method would teach or anticipate our claims and would be good and useful for these purposes. Tollefson and Eli Lilly would also have had the duty to inform the public, the professionals, the media, and regulatory agency (FDA) of any such conclusion, would they have made such a conclusion. They should have especially done that at the time the FDA director in his nationwide front page newspaper interview (and also under prime time media coverage)

was teaching away from our methods. So far they did not do that, despite the very intense and unusual media (and professional) attention on antidepressants' risk of causing suicide, or any of the need of preventive measures thereof. Up to date there is still an unsolved long felt need for the solution that our application can be used for. Please also note the intense legal liability, would a drug company (Tollefson and Eli Lilly, or Chappell and Pfizer) hide such information (risk or solution) that the examiner alleges would be obvious from Tollefson's patent, or from the Chappell's publication. Such a huge legal liability (of not coming forward) had been exemplified by Merck drug company's liability and law suit(s) against them, as also depicted by the media. Merk's first patient lawsuit on Vioxx (causing the death of that patient) resulted in awarding to that single family $253 Million (even if the amount later was reduced). As per my recollection of other news on this topic Merk did not warn the public on the result of prior studies indicating the risk found, but went ahead and repeated the study instead hiding for years the problem [and solution of warning or of withdrawing their drug]). So not only that Tollefson and Eli Lilly (or Chappell and Pfizer) have not disclosed our claims and a solution for a long felt need, their silence is construed of teaching away (of that use).

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.**
If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention**."

As we have shown the prior arts cited does not anticipate our claims, but teach away.

The same reference by Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) discussing obviousness (35 U.S.C. Sec. 103(a)) at page 219 states (referring to MPEP Sec. 706.02(J).) "that references must ... suggest [our] claimed invention, or [the] examiner must present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." We have shown in this extensive reply why the thinking pattern of one skilled in the art would have been different from the examiner's reasoning, and why one skilled in the art could not have disregarded the boundaries of standard of care without adequate guidance, and without going through a risk/benefit/side effect, available alternatives analysis (etc).

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 220 also states, that: "The prior art reference ... must teach or suggest all [our] claim limitations." **As we have shown (including the secondary factors) this is also not the case.**

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 222 teaches that in overcoming rejection based on obviousness, we can argue (and in this reply I think there is no doubt that we successfully did that) that "the combined teaching of the cited **references still fail to fully teach the invention recited herein**". At page 223 it sates: "**If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn**. (In re Rouffet, 149 F.3d 1350 (Fed. Cir.1998).)

As we have shown in Reply-12, secondary factors also apply in regard of prevention of depression and depressive relapse. As secondary factor showing unobviousness of our invention, even more than four (4) years after our application, others with major interests are still not teaching our method.

Enabling:

While **all of the above had shown, that we had put our method in the possession of the skilled in the art (psychiatrist), and that we have done that without the need of undue experimentation,** the following can be specifically revisited:

In re Wands, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The above had shown, that:

Regarding (2) the state of the prior art; sufficient evidence was provided, that one skilled in the art at the time we filed the application would have not come up with the same invention as we did. The teaching away despite of intense media and FDA attention also provides evidence to that fact. However, with off label use, and with the guidance given by us one skilled in the art would be able to practice the invention without undue experimentation.

(4) the predictability or unpredictability of the art: we can say, that with the guidance given by us one skilled in the art would have been able to practice the invention without undue experimentation. Our guidance have strongly shifted the art toward predictability.

(6) the amount of direction or guidance presented: As shown above we have provided an extensive, and sufficient amount of direction or guidance so that someone can practice our invention without undue experimentation. We have discussed risk/benefit alternatives, and reasons to use our method for the prevention of suicide (also taking into account the benefit of the group). We were teaching exactly (within reason) of how to make use of our invention for the various purpose provided. We were also providing hypothetical examples. In addition the skilled in the art knows of how one can use already FDA approved medications off label. Therefore no undue experimentation would be necessary.

(8) the quantity of experimentation necessary: No undue amount of experimentation is necessary, as we have extensively shown in our reply.

Therefore our invention is enabling, does not require undue experimentation.

SUMMARY AND CONCLUSIONS

In view of the foregoing, it is respectfully submitted that the amended claims are supported by an enabling disclosure and are patentable over the applied art. As a result, it is respectfully submitted that Claims 1-39, 41-43 and 48-54 and new Claims 55-118 are in proper form for issuance of a Notice of Allowance and such action is respectfully requested at an early date.

If for any reason you would feel that any of the claims as amended would not be allowed, please schedule a meeting with the Applicant.

The Applicant's cell phone number (voicemail identifying him) is:

(724)840-0464

Please note, that the Applicant have lost his attorney representation, and is relying on your guidance.

Respectfully submitted,

Peter Migaly, M.D. 1/17/07